รายงานวิจัยฉบับสมบูรณ์

โครงการ
การสังเคราะห์ bisindole-triazoles แบบง่ายเพื่อพัฒนาเป็นสารต้านมะเร็ง

Convenient synthesis of bisindole-triazoles
for developing as anticancer agents

รุ่งนภา แซ่เอ็งและคณะ

โครงการวิจัยประเภทงบประมาณเงินรายได้
จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน)
ประจำปีงบประมาณ 2558
มหาวิทยาลัยบูรพา

รหัสโครงการ 177534
สัญญาเลขที่ 62/2558

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10 กันยายน 2559

กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนการวิจัยจากงบประมาณเงินรายได้จากเงินอุดหนุนรัฐบาล
(งบประมาณแผ่นดิน) ประจำปีงบประมาณ พ.ศ. 2558 มหาวิทยาลัยบูรพา
ผ่านสำนักงานคณะกรรมการการวิจัยแห่งชาติ เลขที่สัญญา 62/2558

Acknowledgment

This work was financially supported by the Research Grant of Burapha University through National Research Council of Thailand (Grant no. 62/2558).

สารบัญ

คำนำ

โครงการวิจัย “การสังเคราะห์ bisindole-triazoles แบบง่ายเพื่อพัฒนาเป็นสารต้านมะเร็ง” ได้รับการสนับสนุนทุนการวิจัยงบประมาณแผ่นดินประจำปีงบประมาณ 2558 มหาวิทยาลัยบูรพา รายงานการวิจัยฉบับนี้เสนอรายละเอียดของการวิจัยซึ่งประกอบด้วยบทนำที่เสนอผลงานวิจัยที่เกี่ยวข้อง ผลการทดลองวิจัย การอภิปรายสรุปผล และการตรวจสอบโครงสร้างของสาร

การวิจัย “การสังเคราะห์ bisindole-triazoles แบบง่ายเพื่อพัฒนาเป็นสารต้านมะเร็ง” สำเร็จลุล่วงไปด้วยดี โดยผู้วิจัยต้องขอขอบคุณทีมวิจัยซึ่งประกอบด้วยที่ปรึกษาโครงการ ศ.ดร. อภิชาต สุขสำราญ คณะวิทยาศาสตร์ มหาวิทยาลัยรามคำแหง ศ.ดร. ภาวิณีปิยะ จตุรวัฒน์ มหาวิทยาลัยมหิดล ผู้ร่วมโครงการ ดร.อุทัยวรรณ ศิริอ่อน รวมทั้งนิสิตปริญญาตรี โทและเอกภาควิชาเคมี นางสาวณัฐิยา แซ่หลิม นายธีรพิชญ์ เกษมสุข นางสาวมนัสวี จั่นรอด นางสาวฐาปนี เพชระและนายธีรชาติ เนียมรอด ขอขอบคุณ คุณสุทธิพร พิกุลทอง มหาวิทยาลัยมหิดล ที่ทำการตรวจสอบ High Resolution Mass ของสารสังเคราะห์ที่ได้ งานวิจัยนี้ได้รับการสนับสนุนจากภาควิชาเคมี คณะวิทยาศาสตร์ และศูนย์นวัตกรรมความเป็นเลิศทางเคมี PERCH-CIC

ผศ. ดร. รุ่งนภา แซ่เอ็ง
อาจารย์ประจำภาควิชาเคมี คณะวิทยาศาสตร์
หัวหน้าโครงการวิจัย

บทคัดย่อ

งานวิจัยนี้ได้ทำการวางแผนและสังเคราะห์สารอนุพันธ์ bisindole-triazoles ชนิดใหม่ เพื่อศึกษาฤทธิ์ต้านมะเร็ง ในส่วนแรกของงาน ทีมวิจัยได้ศึกษาและตรวจสอบสภาวะที่เหมาะสมในแต่ละขั้นตอนของการสังเคราะห์โดยเริ่มจากปฏิกิริยา Friedel-Craft alkylation ตามด้วย *N*-propargylation และ click reaction สามารถสังเคราะห์สารผลิตภัณฑ์จำนวน 15 ตัว คือ สารอนุพันธ์ 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**s 4** ใน %yield ที่ปานกลางถึงดี ในส่วนที่สองของงานได้ทำการสังเคราะห์อนุพันธ์ 3,3’-(4-chlorophenylmethylene)-bis-(1-(prop-2-ynyl)-1*H*-indole)triazole โดยทำผ่านสามขั้นตอนของปฏิกิริยาเคมีในหนึ่งหม้อปฏิกิริยา ซึ่งประกอบด้วยปฏิกิริยา Friedel-Craft alkylation ตามด้วย *N*-propargylation และ click reaction สามารถสังเคราะห์สารผลิตภัณฑ์ bisindole-triazoles จำนวน 14 ตัว ใน %yield ที่ปานกลางถึงดีมาก (17-99%) ด้วยวิธีในหนึ่งหม้อปฏิกิริยา

Abstract

In this work, we designed and synthesized two types of new analogues of bisindole-triazoles for further study as anticancer agents. In the first part, we studied and investigated the best conditions for each step of the synthesis starting from Friedel-Craft alkylation, *N*-propargylation and click reaction. Fifteen analogues of desired product 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**s 4** were obtained in fair to good yields. In the second part, the synthesis of 3,3’-(4-chlorophenylmethylene)-bis-(1-(prop-2-ynyl)-1*H*-indole)triazole derivatives were carried out *via* one-pot 3 steps Friedel-Craft alkylation, *N*-propargylation and click reaction. Fourteen bisindole-triazoles were obtained in fair to excellent yields (17-99%) using one-pot procedure.

Chapter 1 Introduction and Literature reviews

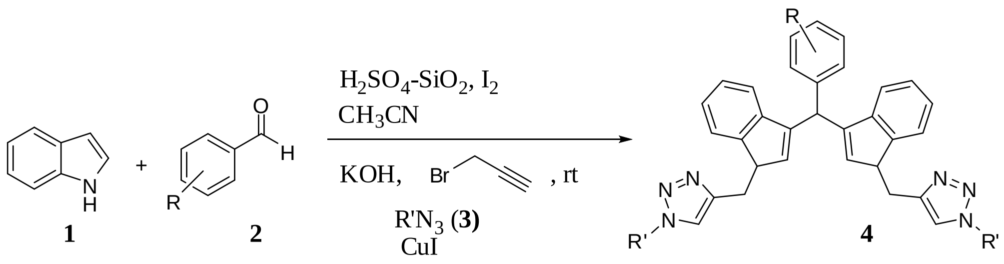
Introduction

Indole and their derivatives have received special attention in pharmaceutical chemistry due to their diverse medicinal potential. The modification of the indoles with various functional groups has gained increasing interested. Wherein, most of reports are focus on C-3 position of the indole structure, this outcome is a result of the high nucleophilic reactivity at the 3-position of the heterocyclic compound (Bandini&Eichholzer, 2009). The Friedel-Crafts alkylation of indoles with aldehyde substrates is a completely atom economical reaction that provides a very useful approach to bisindole derivatives, which received considerable attention because they have potential for biological activity.

Bis(indolyl)methanes possess a wide range of biological activities, their synthesis has received much interest for organic chemist (Damodiran, Muraliharan & Perumal, 2009). Bis(indolyl)methanes are a biologically valuable group of organic compound that have been isolated from earthly and marine natural. They are reported to induce apoptosis in human cancer cell and are found in cruciferous plants. Bis(indolyl)methanes have many applications in material science, agrochemicals and pharmaceuticals. In the recent years, there is a great interest in the synthesis of these compounds (Vahdat, Khaksar & Baghery, 2011).

In addition, 1,2,3-triazoles, classic nitrogen heterocyclic compounds, are used in pharmaceuticals, agrochemicals, dyes and photographic materials etc (Seus et al., 2012, p.10419). They are important compounds in medicinal chemistry owing to their wide applications in drug discovery. 1,2,3-Triazoles is a key structural motif in many bioactive compounds, exhibiting a broad spectrum of biological activities, such as antiviral, anticancer, anti-HIV, antibiotic, antibacterial, and antimicrobial (Rad, Behrous, Doroodmand & Movahediyan, 2012). Several methodologies were then investigated to control the regioselectivity and to improve the reaction conditions for the formation of 1,2,3-triazoles. The copper catalyzed azide alkyne cycloaddition reaction (abbreviated to Cu-AAC) or click chemistry is the well documented, with several published reviews describing the different catalysts and ligands used, including the mechanistic aspects.

Since both indole and triazole structure were previously reported for pharmaceutical properties, therefore, this work was aimed to synthesize of bisindole-triazole derivatives for further investigation of their biological activity. A new class of bis-indole-1,4-disubstituted-1,2,3-triazoles derivatives was designed to prepare in one-pot three steps *via* Friedel-Crafts reactions, *N*-propargylation and the click reaction (Scheme 1).



Scheme 1 Synthesis of bisindole triazoles in this work

Literature reviews

The various derivatives of indoles and bis(indolyl)methanes are important intermediates in organic synthesis and have wide medicinal applications such as to induce apoptosis in human cancer cells and normalize abnormal cell growth associated with cervical dysplasia, to promote beneficial estrogen metabolism in both women and men, to prevent breast cancer and also to increase the natural metabolism of the body's hormones (Mulla et al., 2012).

1,2,3-Triazoles is one of the most powerful click reactions. 1,2,3-Triazole and their derivatives synthesis has been intensively studied and widely used in pharmaceuticals, agricultural, material science and biology including anti-HIV, anticancer and antimicrobial activities (Damodiran, Muralidharan & Perumal, 2009).

Due to the vast biological activity of bis(indolyl)methanes and 1,2,3-triazoles and their wide medicinal applications, various methods of their synthesis have been developed and new approaches are still appearing in the literature as follows.

Selected examples of the synthesis bis(indolyl)methanes or 3,3'-(phenylmethylene)bisindole

Vahdat, Khaksar and Baghery (2011) reported a new methodology for the synthesis of bis(indolyl)methanes from one-pot condensation of various aldehyde or ketone with indole using non-volatile ionic liquid with multi-SO_3H groups (Figure2-1) as a catalyst under ambient temperature (Figure2-2). The ionic liquid catalyst offers several advantages including mild reaction conditions, shorter reaction times, high yield of the products, lower catalytic loading able to reused easily for six-time experiments with a small decrease in the catalytic activity of the recovered catalyst. This method was high chemoselectivity of aldehyde group that demonstrated by a competitive reaction between benzaldyhyde and acetophenone with indole (Figure 2-3).

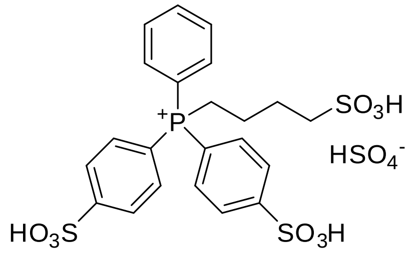


Figure 2-1 ILs with multi SO_3H groups

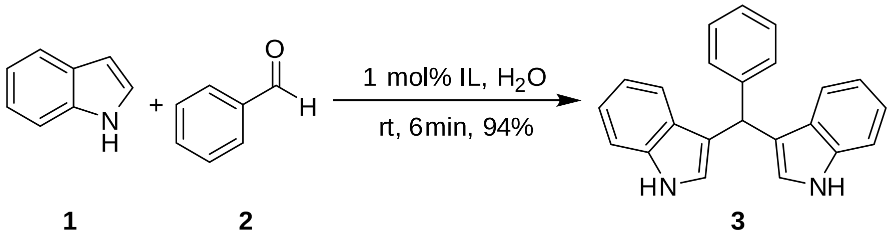


Figure 2-2 Synthesis of bis(indolyl)methane **3** using non-volatile ionic liquid

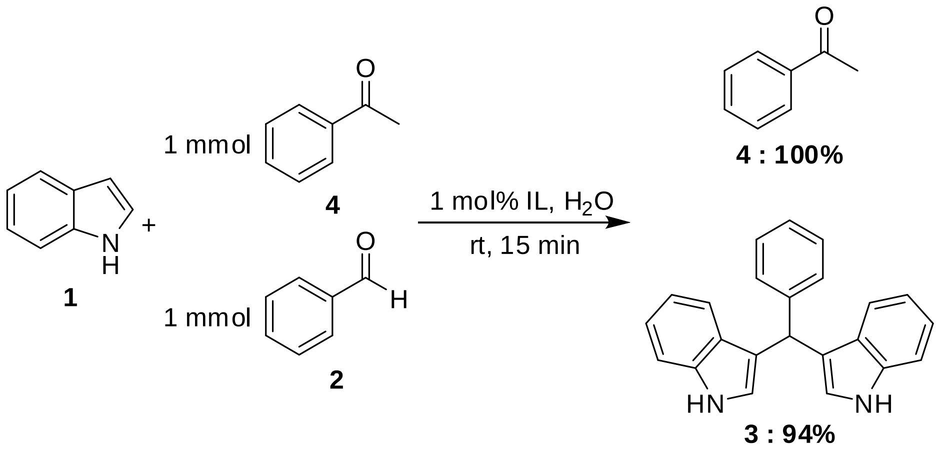


Figure 2-3 Chemoselectivity of indole **1** in reaction with benzaldehyde **2** in presence of acetophenone **4**

Hojati, Zeinali and Nematdoust (2012) developed a simple, novel and efficient method for synthesis of bis(indolyl)methanes in good to excellent isolated yield with chemoselectivity from reactions of indole and carbonyl groups in the presence of DBDMH (1,3-dibromo-5,5-dimethylhydantoin) as a highly efficient, commercial available and inexpensive catalyst under solvent-free conditions (Figure 2-4, 2-5, 2-6).

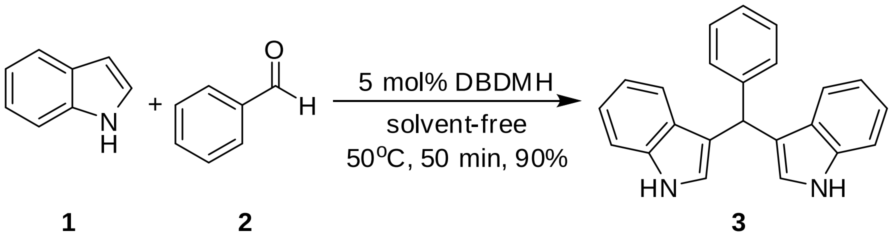
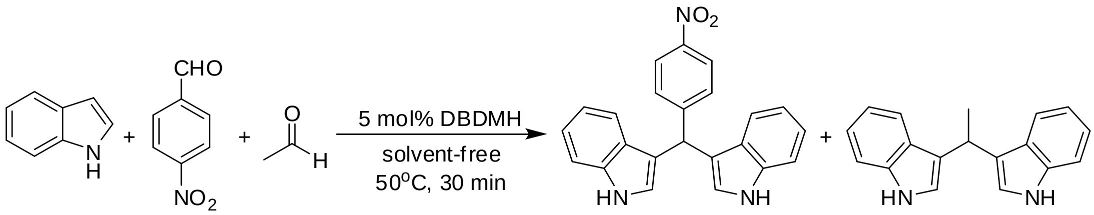


Figure 2-4 Synthesis of bis(indolyl)methane **3** in the presence of DBDMH

The equimolar mixtures of p-nitrobenzaldehyde **4** and acetaldehyde **5** (Figure 2-5) and also p-nitrobenzaldehyde **4** and cyclohexanone **8** (Figure 2-6) were prepared and reacted with indole **1** in the presence of DBDMH under optimum reaction conditions. It was observed that aromatic aldehyde produced corresponding bis(indolyl)methane as major product in both reactions and another substrate remained intact in the reaction mixture.

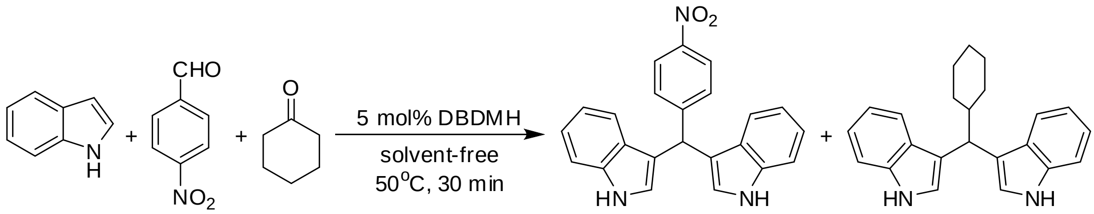
Therefore, the present method is potentially applicable for the chemoselective conversion of aromatic aldehydes to corresponding bis(indolyl)methanes in the presence of aliphatic aldehydes and ketones.



1 4 5 6 7

90% 0%

Figure 2-5 The competitive reaction in the presence of DBDMH between p-nitrobenzaldehyde **4** and acetaldehyde **5** with indole **1**.

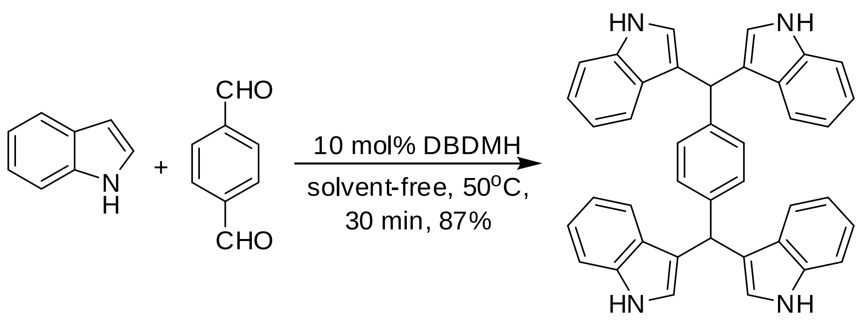


1 4 8 6 9

90% 0%

Figure 2-6 The competitive reaction in the presence of DBDMH between p-nitrobenzaldehyde **4** and cyclohexanone **8**

Furtheremore, di(bis(indolyl)methyl)benzene **11** can be achieved by this method. The reaction of terephthalaldehyde **10** with 4 equiv. of indole **1** was performed in the presence of DBDMH (10 mol %) under optimized conditions and p-di(bis(indolyl)methyl)benzene **11** produced in 87% yields after 90 min (Figure 2-7).



1 10 11

Figure 2-7 Synthesis of bis(indolyl)methane **3** in the presence of DBDMH terephthalaldehyde **10**

The preparation of bis(indolyl)methane induced by DBDMH can be rationalized by the following mechanism (Figure 2-8).

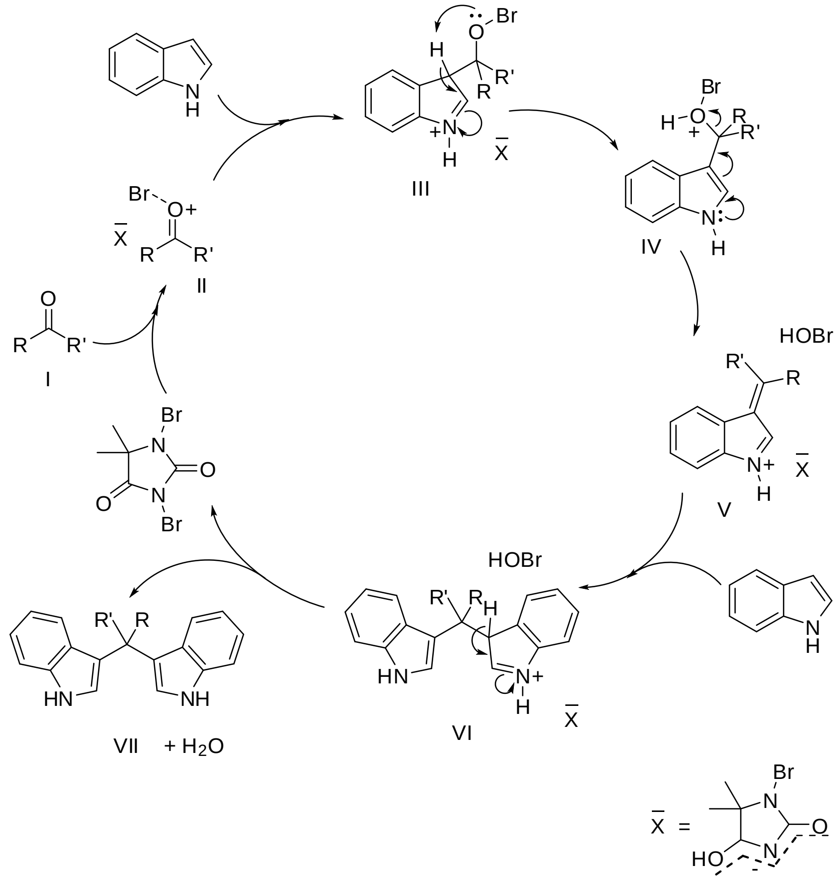


Figure 2-8 Mechanism of the preparation of bis(indolyl)methane using DBDMH as a catalyst

Initially, the carbonyl group of aldehyde or ketone is activated by brominium ion. Then, nucleophilic attack of indole to activated carbonyl group II produces azafulvenium salt V. The formation of azafulvenium salt confirms by selectivity of the reaction as aromatic aldehydes can produce a stable conjugated system in azafulvenium salt but aliphatic aldehydes can’t, so, aromatic aldehydes react faster than aliphatic ones. And finally, nucleophilic attack of second indole to V lead to the corresponding bis(indolyl)methane VII and the catalyst return to the next catalytic cycle.

Ghodrati et al. (2013) developed the preparation of bis(indolyl)methanes via condensation of indoles with various carbonyl compounds in the presence of nanosilica gel as catalyst under ultrasonic irradiation 80°C. The product was obtained in good to excellent yields in solvent-free condition. This methodology is simplicity in operation and green aspects by avoiding toxic catalysts and solvents. Silica nanoparticle catalyst can be recovery and recycling (Figure 2-9).

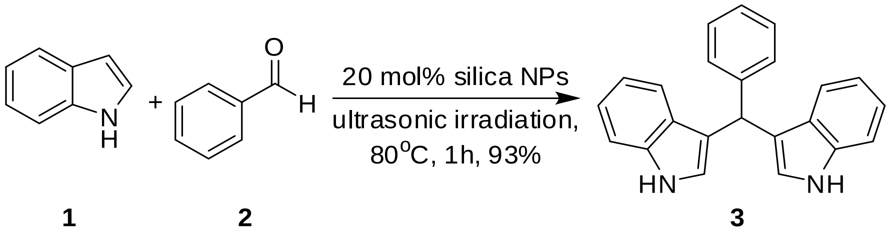
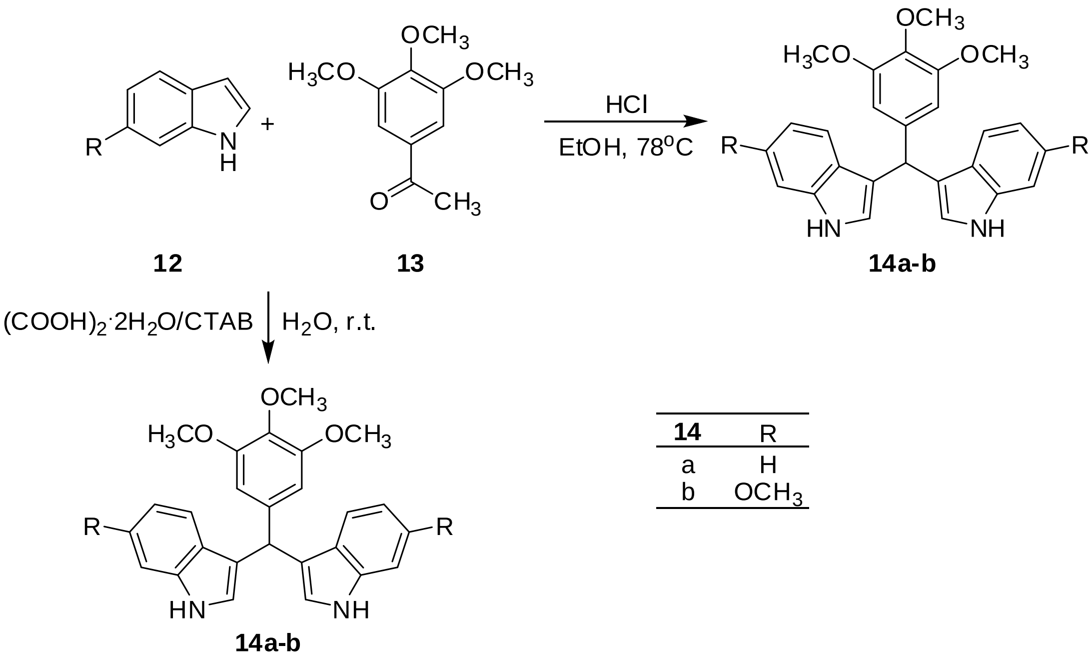


Figure 2-9 Synthesis of bis(indolyl)methane **3** using nanosilica gel as catalyst under ultrasonic irradiation 80°C

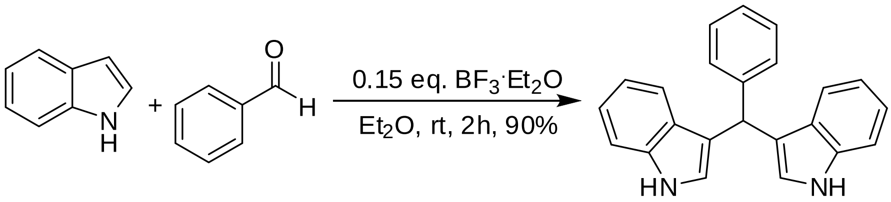
Marrelli et al. (2013) reported the synthesis of bis(indolyl)methane derivatives with different indoles and trimethoxyacetophenone that provided new compounds. First reaction was employed hydrochloric acid as a catalyst and second reaction was employed oxalic acid dihydrate ($(CO_2H)_2{\cdot}2H_2O$) and *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (CTAB) (Figure 2-10). Compound **14b** seems to be a promising compound potentially useful as anticancer agent, and further modifications of this molecule will be carried out in order to optimize the activity.



14	R
a	H
b	OCH_3

Figure 2-10 Synthesis of bis(indolyl)methanes **14a** and **14b**. **14a**: R = -H; **14b**: R = -OCH_3. Reagents and conditions: (a) HCl, EtOH, 78^{o}C, 19 and 22 h for **14a** and **14b**, respectively. (b) $(COOH)_2{\cdot}2H_2O$/CTAB, H_2O, room temperature, 7 and 10 h for **14a** and **14b**, respectively

Xu et al. (2013) have reported the synthesis of bis(indolyl)methanes using $BF_3 \cdot Et_2O$ as an efficient catalyst for electrophilic substitution reactions of indoles and carbonyl compounds with isolated yields up to 96%. There is mild and metal-free reaction conditions render this methodology a practical protocol (Figure 2-11).

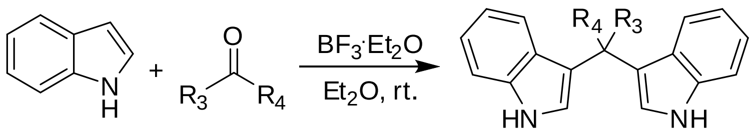


1 **2** **3**

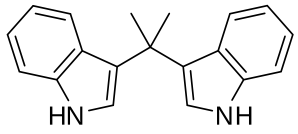
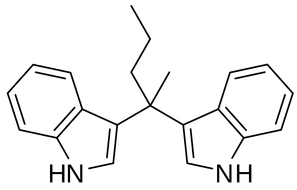
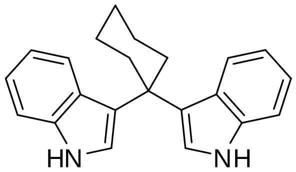
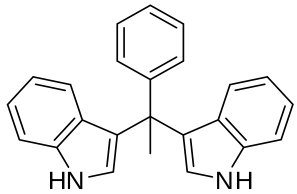
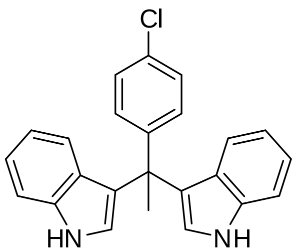
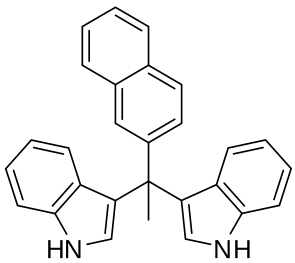
Figure 2-11 Synthesis of bis(indolyl)methane **3** using $BF_3 \cdot Et_2O$ as a catalyst

In this paper, the less reactive ketonic substrates were report to evaluate this methodology with indoles. Aliphatic ketones such as acetone **15a** and 2-pentanone **15b** were examinated and gave moderate yields over 24h. It is noteworthy that cyclohexanone provide the target product **16c** in 81% yield. In the case of aromatic ketones **16d-f**, yields of 9%, 35% and 11% were obtained, respectively (Table 2-1).

Table 2-1 Reaction of indole with ketones catalyzed by $BF_3 \cdot Et_2O$[a]



1 **15** **16**

Entry	Ketone	Product	Time (h)	Yield (%)[b]
1	**15a**	 **16a**	29	56
2	**15b**	 **16b**	10	16
3	**15c**	 **16c**	2	81
4	**15d**	 **16d**	24	9
5	**15e**	 **16e**	40	35
6	**15f**	 **16f**	40	11

[a] Reaction condition: ketones **15** (1 mmol), indole (2 equiv.) and $BF_3 \cdot Et_2O$ (0.15 equiv.) in Et_2O at room temperature

[b] Isolated yields

The preparation of bis(indolyl)methane induced by $BF_3{\cdot}Et_2O$ can be rationalized by the following mechanism (Figure 2-13). The initial step of the mechanism is the interaction between $BF_3{\cdot}Et_2O$ and analog A to form the complex B, as in the R_2CO-BF_3 complex, and then a molecule of indole attacks B to generate intermediate C, as in the R_3N^{-} BF_3 complex. Through the strong interaction between nitrogen and $BF_3{\cdot}Et_2O$ in C, an elimination of a molecule H_2O is accelerated, and intermediate C is transformed into D. Subsequently, another molecule indole is reacted with D via an aza-Michael addition to afford complex E. With a molecule $BF_3{\cdot}Et_2O$ released, the bis(indolyl)methane F is produced, and the catalyst $BF_3{\cdot}Et_2O$ then enters another catalytic cycle.

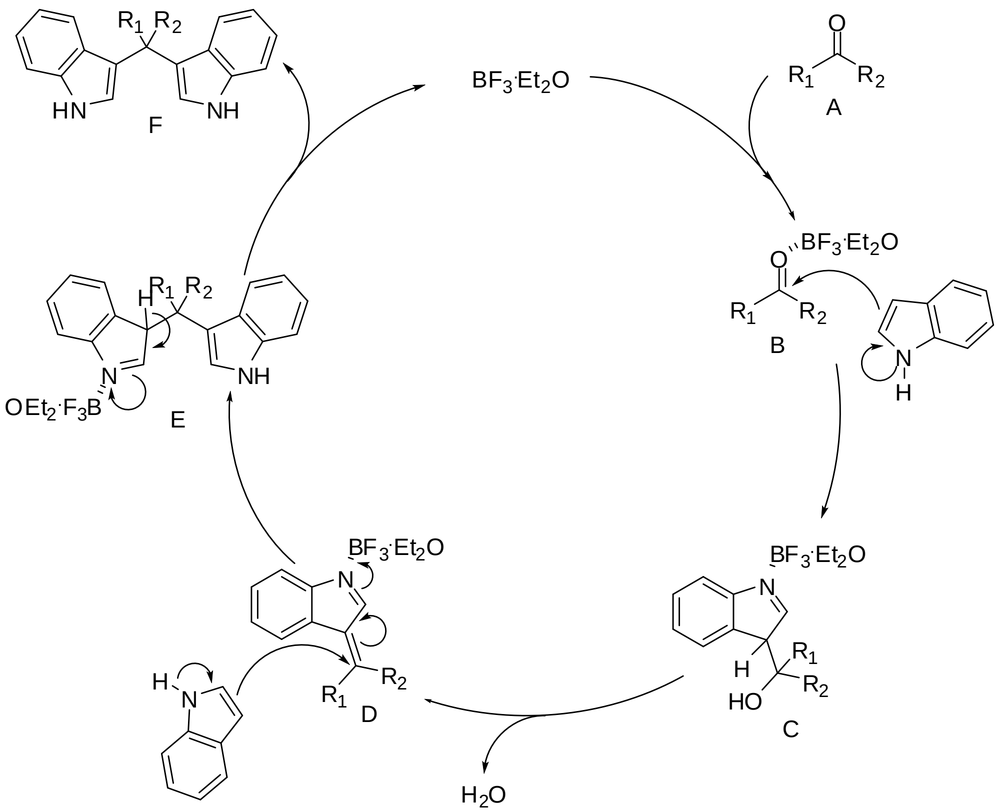
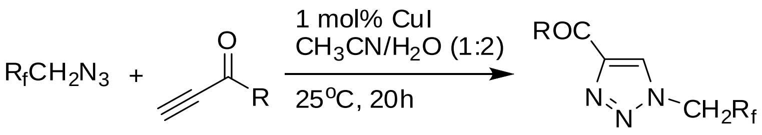


Figure 2-12 A proposed mechanism for the synthesis of indoles with different carbonyl compounds

Selected examples of the synthesis 1,2,3-triazole via 1,3-dipolar cycloaddition click reaction

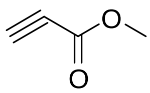
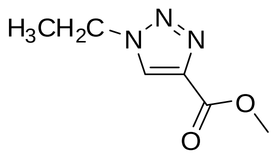
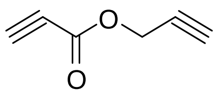
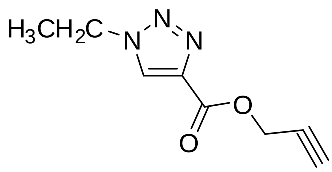
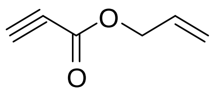
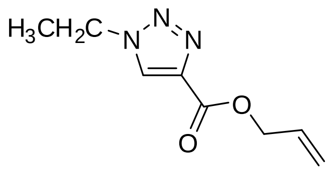
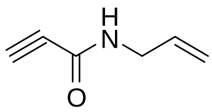
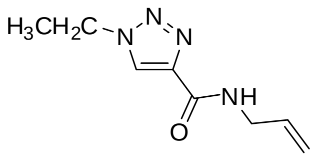
Wu, Deng, Fang and Chen (2004) developed a general method for the synthesis of fluoroalkyled 1,4-disubstituted 1,2,3-triazole by a regioselective 1,3-dipolar cycloaddition of terminal alkynes of propionic esters with fluoroalkylazides catalyzed by Cu(I) salt in moderate to good yield (Figure 2-13 and Table 2-2).



17 **18** **19**

Figure 2-13 Reaction in aqueous and organic media

Table 2-2 The reaction of propiodic esters with fluoroalkyl azides

Entry	Azides	Alkyne	Product	Yield (%)
1	**17a** $CF_3CH_2N_3$	**18a** 	**19a** 	58
2	**17a** $CF_3CH_2N_3$	**18b** 	**19b** 	42
3	**17a** $CF_3CH_2N_3$	**18c** 	**19c** 	69
4	**17a** $CF_3CH_2N_3$	**18d** 	**19d** 	49

It was interesting to note that, high selectivity of the two triple bonds was observed for propiolic ester **18b**. If one equivalent of azide was added, the triple bond of propiolic acid participated in the reaction. No product reacted with the triple bond of propargyl alcohol was detected. If two equivalents of azide was added, then both triple bonds in the substrate reacted with azide, bis-1,2,3-triazole **20** was formed (Figure 2-14).

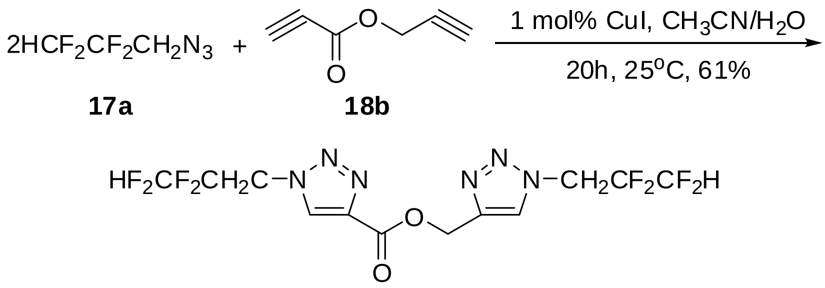


Figure 2-14 1,3 dipolar cycloaddition of azides and alkynes catalysed by CuNPs

Alonso, Moglie, Radivoy and Yus (2009) have introduced a catalytic system, based on CuNPs, that effectively catalyses the 1,3-dipolar cycloaddition of a variety of azides and terminal alkynes furnishing the corresponding 1,2,3-triazoles in excellent yields (88-98%) (Figure 2-15).

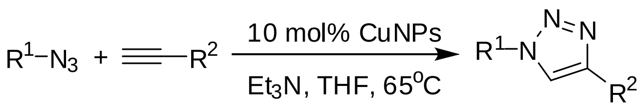
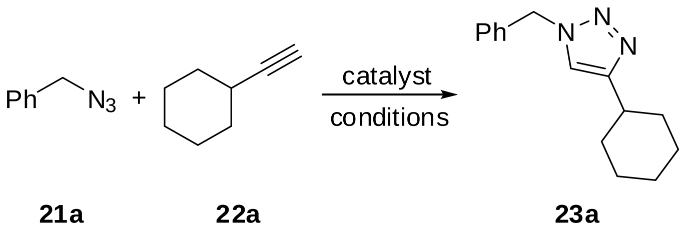


Figure 2-15 1,3 dipolar cycloaddition of azides and alkynes catalysed by CuNPs

Benzyl azide **21a** and cyclohexylacetylene **22a** were used as model substrates in order to optimize the reaction conditions (Table 2-3). Two blank experiments carried out in the absence of Cu but under the conditions of generation of the CuNPs (with or without Et_3N) led to the starting **21a** and **22a**. The presence of Et_3N was shown to be indispensable for the reaction to take place (Table 2-3, entry 1). The CuNPs in stoichiometric amounts were shown to be superior to other sources of copper, leading to **23a** in the highest yield and shortest reaction time (Table 1, entries 2–6). The product yields were also excellent by decreasing the amount of CuNPs up to 1 mol %, albeit longer reaction times were required (Table 1, entries 7-11).

Table 2-3 Examples of the copper-catalyzed 1,3 dipolar cycloaddition of benzyl azide and cyclohexylacetylene[a].



Entry	Catalyst (mol%)	Additive (mmol)	Temp. (°C)	Time (h)	Yield (%)[b]
1	CuNPs (100)	None	25	12	0
2	CuNPs (100)	Et_3N (1)	25	1	98
3	Cu (100)[c]	Et_3N (1)	25	2	0
4	Cu_2O (100)	Et_3N (1)	25	2	0
5	$CuCl_2$ (100)	Et_3N (1)	25	2	0
6	CuCl (100)	Et_3N (1)	25	2	0
7	CuNPs (20)	Et_3N (1)	25	6	98
8	CuNPs (10)	Et_3N (1)	25	6	98
9	CuNPs (5)	Et_3N (1)	25	24	98
10	CuNPs (2)	Et_3N (1)	25	24	100
11	CuNPs (1)	Et_3N (1)	25	24	100

[a] **21a** (1 mmol) and **22a** (1 mmol) in THF
[b] GLC yield
[c] Cu powder (1-5 μm)

González et al. (2011) showed appropriate conditions for alkynes and azides that efficiently converted into 1,2,3-triazoles or bistriazoles through variations of temperature and NaOH concentration. Temperature is an important factor in the copper catalyzed alkyne azide cycloaddition under oxidative conditions. 1,2,3-Triazoles were obtained in high yields when several alkynes and azides were reacted at methanol reflux using catalytic amounts of both copper iodide and sodium hydroxide. On the other hand, bistriazoles **27** were major products when reactions were performed at -35°C using excess sodium hydroxide (Figure 2-16).

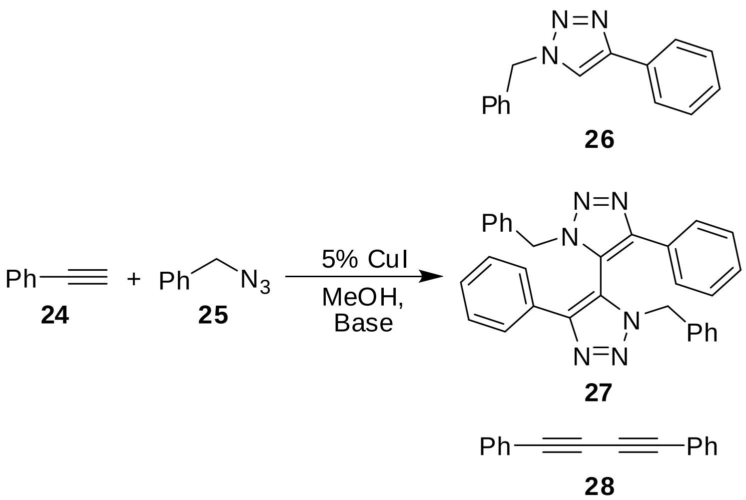
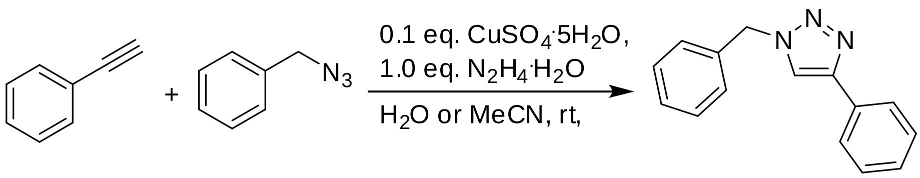


Figure 2-16 Cu-catalyzed cycloaddition between alkyne **24** and azide **25**

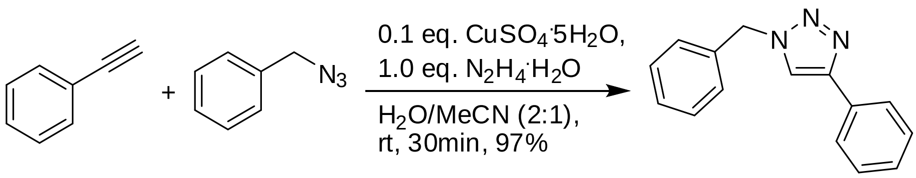
Pathigoolla, Pola, & Sureshan (2012) presented a novel and high yielding methodology for room temperature azide–alkyne click cycloaddition using in situ generated CuNPs/clusters as the active catalyst which no requirement of stabilizer/support. This reaction can be carried out in open air condition and requires no special reaction conditions and chromatographic separation. The versatility of this methodology has been illustrated by the facile reaction of a variety of azides such as aliphatic, aromatic, benzylic and glycosyl azides with diverse alkynes. This methodology is very attractive as it can be adopted in aqueous (Figure2-17), organic (Figure2-17), mixed solvent (Figure2-18) and solvent-free (Figure2-19) conditions.



24 **25** **26**

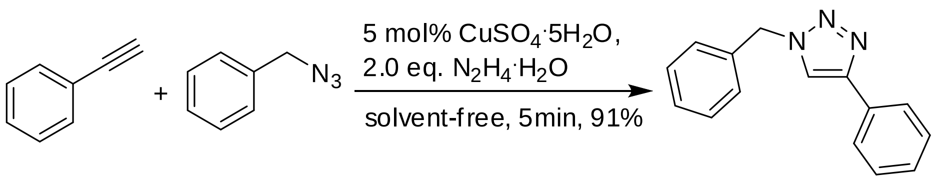
45 min, 95% : water
17 h, 98% : MeCN

Figure 2-17 Reaction in aqueous and organic media conditions



24 **25** **26**

Figure 2-18 Reaction in solution conditions



24 **25** **26**

Figure 2-19 Reaction solvent-free conditions

Selected example of the synthesis *N*-propargyl bis(indolyl) methanes or 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole

Damodiran, Muralidharan, Parammasivan and Perumal (2009) developed a new methodology for the synthesis and biological evaluation of diverse heterocyclic compound. *N*-propargyl bis(indolyl)methanes were synthesized via 1,3-dipolar cycloaddition with sodium azide using CuI as a catalyst in polyethyleneglycol-400. The synthesized compounds have also been screened for antibacterial and antifungal activity. The method is mild reaction condition, safe and efficient for the generation of 1,4-disubstituted 1,2,3-triazole in a complete regioselective manner, avoids isolation, handling of potential unstable organic azide, providing triazole pure form in high yields (Figure 2-20), Compound **29** showed good activity (20mm inhibition) against *S. aureus* (Table 2-4).

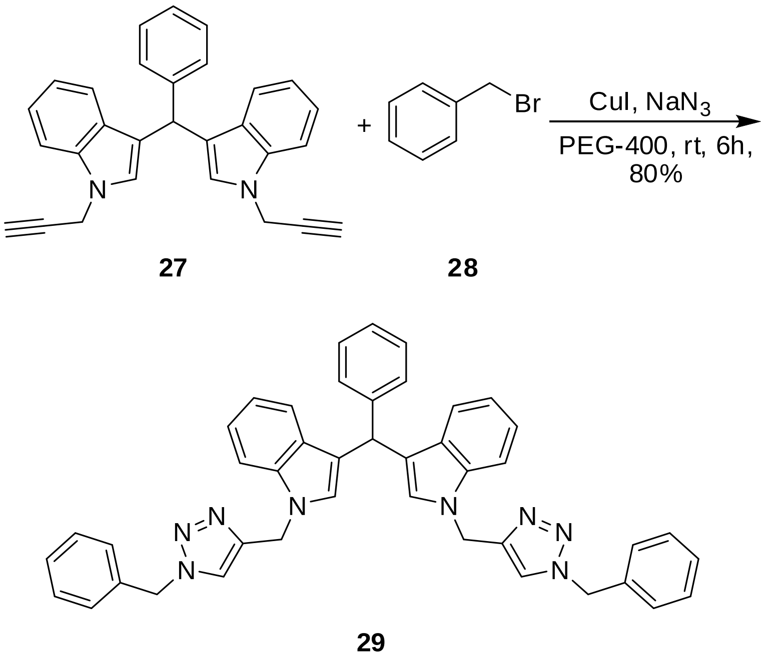


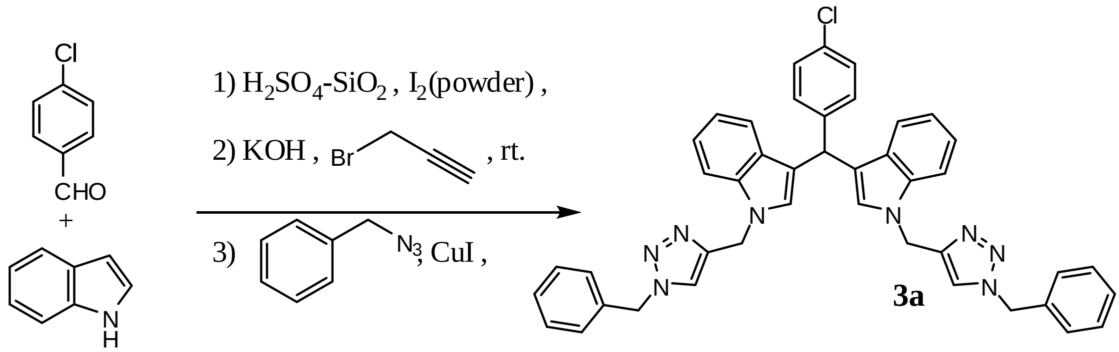
Figure 2-20 Synthesis of 1,2,3-triazole derivatized bis(indolyl)methane **29**

Table 2-4 The antibacterial and antifungal screening data

Compound	Zone of inhibition (in mm)	
	Antibacterial activity *S, aureus*	Antifungal activity *C. albicans*
29	20	16
Ciprofloxacin	22	-
Ketoconazole	-	24

Chapter 2: Results and Discussions

In this research, we designed to synthesize bisindole-triazole and investigate the possibility of performing the one-pot three-steps sequence. The reactions were carried out involving Friedel-Crafts reactions of indoles **1** with aldehyde **2** followed by *N*-propargylation of the resulting bisindole with propargyl bromide and the click reaction of alkyl azides to obtain bis-indole-1,4-disubstituted-1,2,3-triazoles (Scheme 1).



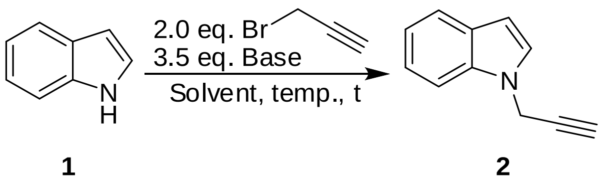
Scheme 1 One pot synthesis analogues of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole

Part 1 Optimization studies for each steps of Friedel-Crafts reactions, *N*-propargylation and Click reactions

To perform the one-pot three-steps sequence, the reaction condition was studied to find the best condition for each step. In the beginning of the project, we studied and optimized the condition of *N*-propargylation.

-Optimization studies for *N*-propargylation

We investigate the synthesis of 1-(prop-2-ynyl)-1H-indole **2** *via* *N*-propargylation reaction from readily available indole **1** and propargyl bromide.



1 **2**

In order to optimize the reaction conditions, including bases, solvents, and temperature, the reaction of indole **1** and propargyl bromide (2.0 equiv) was selected as a model reaction in different conditions. The results are listed in Table 1. The initial reaction using KOH in CH_3CN at room temperature for two hours afforded 1-(prop-2-ynyl)-1H-indole

2 in 70 %yield (Table 1, Entry 1). In entry 2, the reaction was carried out by NaOH for twenty-four hours gave product **2** in 49 %yield (Table 1, Entry 2). By using NaOH in CH_3CN at 50°C for twenty-four hours, the product **2** was obtained in 67% yield (Table 1, Entry 3). By using NaOH in 1.0 mL of CH_3CN at room temperature for twenty-four hours, the product **2** was obtained in 57% yield (Table 1, Entry 4). By using KOH in H_2O at room temperature for twenty-four hours, no any reaction conversions were observed on TLC. By using KOH in CH_3CN at room temperature for twenty-four hours, no any conversions on TLC (Table 1, Entry 5). In the last entry, the reaction was carried out in THF for one hundred twenty hours gave product **2** in 47% yield (Table 1, Entry 6).

Table 1 Synthesis of 1-(prop-2-ynyl)-1H-indole **2** under various conditions

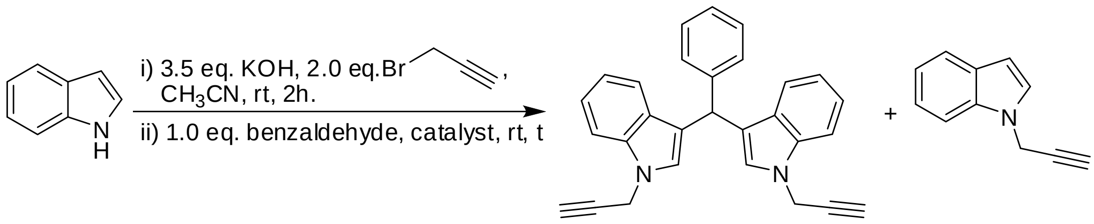
Entry	Base	Solvent	Temp.	Time	Yield (%)
1	KOH	CH_3CN	r.t.	2h	70
2	NaOH	CH_3CN	r.t.	24h	49
3	NaOH	CH_3CN	50°C	24h	67
4[a]	NaOH	CH_3CN	r.t.	24h	57
5	KOH	H_2O	r.t.	24h	no rxn.
6	KOH	THF	r.t.	120h	47

[a] CH_3CN 1.0 mL

As shown in Table 1, the optimum reaction conditions were determined as following: KOH, CH_3CN (2.0 mL) were used as base and solvent at room temperature (Table 1, Entry 1).

-Optimization studies for *N*-propargylation and Friedel-Crafts reaction using various catalysts

Subsequently, we studied the synthesis of 3,3'-(phenylmethylene) bis(1-(prop-2-ynyl)-1H-indole) **3** *via* one-pot *N*-propargylation by using the optimized condition, and Friedel-Crafts reaction from readily available benzaldehyde.



For the first step, the reaction was carried out by the optimum reaction condition from entry 1 of Table 1. The second step of Friedel-Crafts reaction, benzaldehyde (1.0 equiv) was selected as a model reaction in different conditions. The results are listed in Table 4-2. The initial reaction using 10 mol% of I_2 for eighteen hours afforded 1-(prop-2-ynyl)-1H-indole **2** in 44% yield (Table 2, Entry 1). In entry 2, the reaction was carried out by 10 mol% of $InCl_3$for eighteen hours gave product **2** in 44% yield (Table 2, Entry 2). By lowering used 10 mol% of CdI_2 for eighteen hours, the product **2** was obtained in 30% yield (Table 2, Entry 3). By lowering used 10 mol% of $ZnCl_2$ for eighteen hours, the product **2** was obtained in 50% yield (Table 2, Entry 4). By lowering used 20 mol% of $ZnCl_2$ for four hours, the product **2** was obtained in 63% yield (Table 2, Entry 5). In the last entry, the reaction was carried out by 50 mol% of $ZnCl_2$ for four hours, the product **2** was obtained in 54% yield (Table 2, Entry 6). Compound **3** was not obtained from any reactions in Table 2.

Table 2 Synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) **3** under various conditions

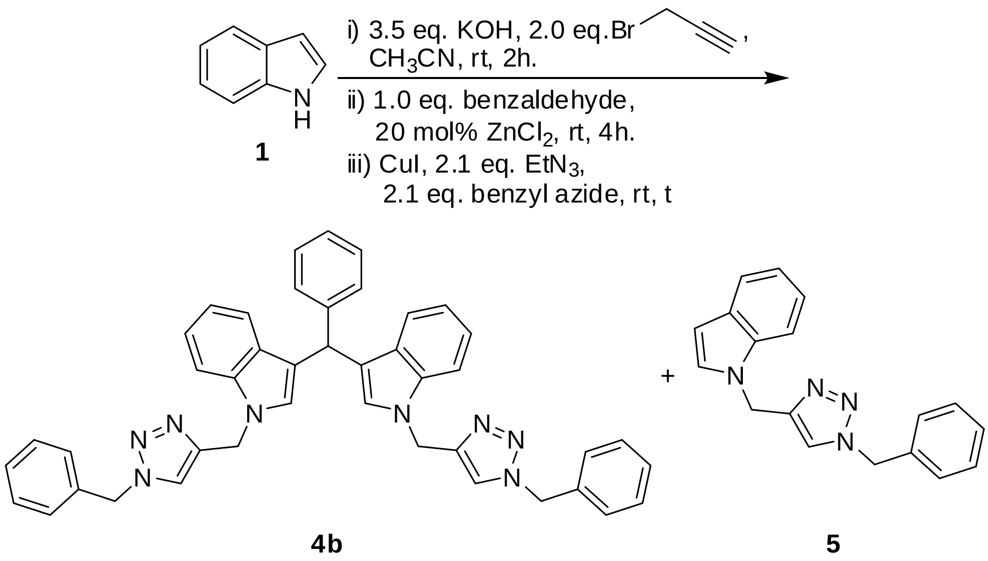
Entry	Catalyst (mol%)	Time (h)	Yield (%)	
			Compound **2**	Compound **3**
1	I_2 (10)	18	44	0
2	$InCl_3$ (10)	18	44	0
3	CdI_2 (10)	18	30	0
4	$ZnCl_2$ (10)	18	50	0
5	$ZnCl_2$ (20)	4	63	0
6	$ZnCl_2$ (50)	4	54	0

As shown in Table 2, the optimum reaction conditions were determined using 20 mol% of $ZnCl_2$ as a catalyst at room temperature (Table 2, Entry 5).

The optimized reaction condition was used in the second step (Friedel-Crafts reaction) of the synthesis of 3,3'-(phenylmethylene) bis(1-(prop-2-ynyl)-1H-indole) triazole*via* one-pot *N*-propargylation, Friedel-Crafts reaction and 1,3-dipolar cycloaddition click reaction.

-Optimization studies for one-pot *N*-propargylation, Friedel-Crafts reaction and 1,3-dipolar cycloaddition click reaction using various catalysts

We investigated the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole **4b** *via* one-pot *N*-propargylation, Friedel-Crafts reaction, used the optimized condition, and 1,3-dipolar cycloaddition click reaction from readily available benzyl azide.



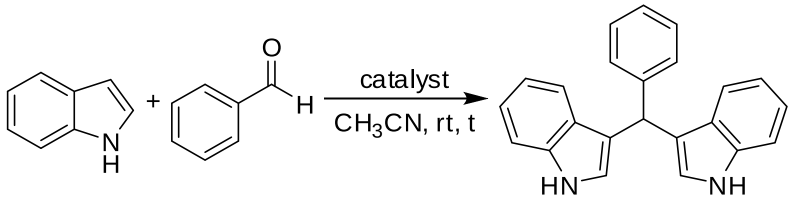
The first step and the second step of the reaction were carried out by the optimum reaction condition from entry 1 of Table 1 and entry 5 of Table 2, respectively. The third step of 1,3-dipolar cycloaddition click reaction, benzyl azide (2.1 equiv) was selected as a model reaction in different conditions. The results are listed in Table 3. The initial reaction using 10 mol% of CuI for 30 minutes afforded 1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole **5** in 41% yield (Table 3, Entry 1). In entry 2, the reaction was carried out by 25 mol% of CuI for 1 minute gave product **5** in 75% yield (Table 3, Entry 2). By using 50 mol% of CuI for one minute, the product **5** was obtained in 64% yield (Table 3, Entry 3). In the last entry, the reaction was carried out by 25 mol% of CuI for 30 minutes, the product **5** was obtained in 33% yield (2, Entry 4). Compound **4b** was not obtained from any reactions in Table 3.

Table 3 Synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**4b** under various conditions

Entry	CuI (mol%)	Additive	Time (min)	Yield (%)	
				Compound **4b**	Compound **5**
1	10	Et_3N	30	0	41
2	25	Et_3N	1	0	75
3	50	Et_3N	1	0	64
4	25	-	30	0	33

As shown in Table 3, the target compound **4b** was not obtained from reactions using $ZnCl_2$ as a catalyst in Friedel-Crafts reaction. Then, we investigated new catalyst for performing the reaction, however the reaction condition in the last step (1,3-dipolar cycloaddition click reaction) was optimized using 25 mol% of CuI and Et_3N at room temperature (Table 3, Entry 2).

-Optimization studies for the synthesis of 3,3'-(phenylmethylene)bisindole *via* Friedel-Crafts reaction using various catalysts



1 **6** **7**

We investigated the synthesis of 3,3'-(phenylmethylene)bisindole **7** *via* Friedel-Crafts reaction from readily benzaldehyde **6** and CH_3CN using various catalysts. The reaction of indole **1** and benzaldehyde **6** was selected as a model reaction in different conditions. The results are listed in Table 4. The initial reaction using 20 mol% of $ZnCl_2$ in CH_3CN at room temperature for 26 hours, bisindole **7** was not obtained in this reaction (Table 4, Entry 1). In entry 2, the reaction was carried out by H_2SO_4-SiO_2 for 24 hours, the product **7** was not obtained in this reaction (Table 4, Entry 2). In the last entry, the reaction was carried out by H_2SO_4-SiO_2/I_2 for 30 minutes gave product **7** in 52% yield (Table 4, Entry 3).

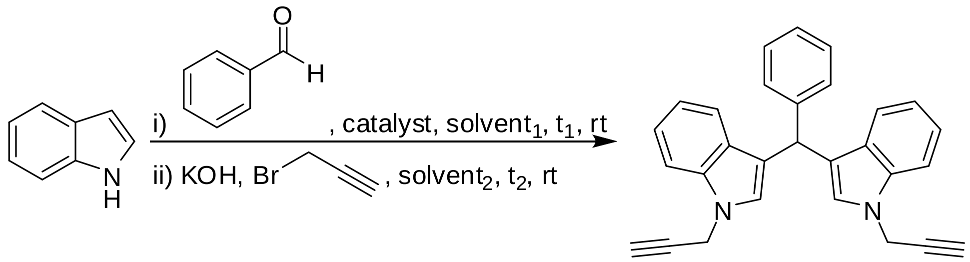
Table 4 Synthesis of 3,3'-(phenylmethylene)bisindole **7** under various conditions

Entry	Catalyst (mol%)	Time	Yield (%)
1	$ZnCl_2$ (20)	26 h	0
2	H_2SO_4-SiO_2[a]	24 h	no rxn.
3	H_2SO_4-SiO_2[a] / I_2 (20)	30 min	52

As shown in Table 4, the optimum reaction conditions were carried out using H_2SO_4-SiO_2/I_2 as catalysts at room temperature (Table 4, Entry 3). This optimized reaction condition was used for the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) *via* one-pot reaction.

-Optimization studies for the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) *via* one-pot Friedel-Crafts reaction and *N*-propargylation reaction under various catalysts and solvents.

We studied the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) **3** by changing the order of reactions by performing Friedel-Crafts reaction in the first step followed by *N*-propargylation.



1 **3**

The reaction was carried out from readily available indole **1**, benzaldehyde, KOH and propargyl bromide. In order to optimize reaction conditions, catalysts and solvents was optimized in each reaction. The first step of Friedel craft reaction of indole **1** and banzaldehyde was selected as a model reaction in different conditions followed by *N*-propargylation, propargyl bromide was selected as a model reaction in different conditions. The results are listed in Table 5. The initial reaction using I_2 powder and H_2SO_4-SiO_2 in CH_3CN at room temperature for 15 minutes in the first step and 24 hours in the second step, 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) product **3** was not obtained in this reaction (Table 5, Entry 1). In entry 2, the reaction was carried out by I_2 powder for 45 minutes, the product **3** was not obtained from this reaction (Table 5, Entry 2). By using 20 mol% of I_2 powder in toluene in the first step for 1 hour and used CH_3CN in the second step for 20 hours, the product **3** was obtained in 60% yield (Table 5, Entry 3). In the last entry 20 mol% of I_2 pellet and H_2SO_4- SiO_2 for 45 minutes in the first step and 44 hours in the second step, the product **3** was obtained in 41% yield (Table 5, Entry 4).

Table 5 Synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) **3** under various conditions

Entry	Catalyst (mol%)	$Solvent_1$	$Solvent_2$	t_1 (h)	t_2 (h)	Yield (%)
1	H_2SO_4-SiO_2[a] / I_2 powder (20)	CH_3CN	-	0.25	24	-[b]
2	I_2 powder (20)	CH_3CN	-	0.75	0.75	-[c]
3	I_2 powder (20)	Toluene	CH_3CN	1	20	60
4	H_2SO_4-SiO_2[a] / I_2 pellet (20)	Toluene	CH_3CN	0.75	44	41

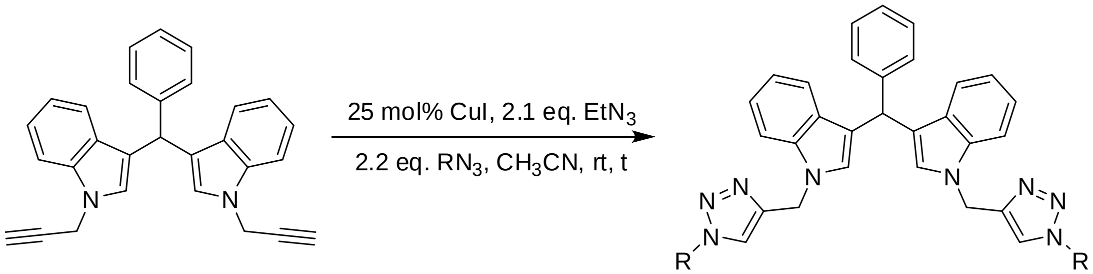
[a] H_2SO_4-SiO_2 used 70-80 mg
[b] No reaction was observed in the second step
[c] Significant peak was not showed in crude nmr spectrum

As shown in Table 5 Entry 3, this optimized reaction condition was used in the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) **3**. Compound **3** was used as a precursor in the synthesis analogues of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole *via* 1,3-dipolar cycloaddition click reaction.

Synthesis analogues of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole*via* 1,3-dipolar cycloaddition click reaction under optimized reaction condition.

With compound **3** in hand, we synthesized 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole *via* 1,3-dipolar cycloaddition click reaction by carrying out the reaction using a variety of azides. As shown in Table 6, a wide range of azides gave the desired product 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**s 4a-4o** in fair to high yields.

Table 6 Synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole)triazole **4** *via* 1,3-dipolar cycloaddition click reaction.



3 **4**

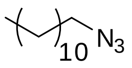
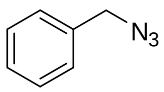
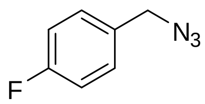
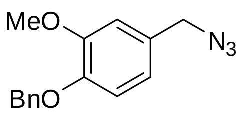
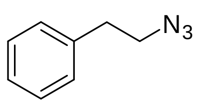
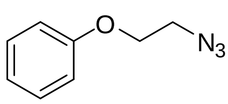
Entry	Azide	Time (min)	Product	Yield (%)
1		20	**4a**	88
2		5	**4b**	98
3		60	**4c**	79
4		25	**4d**	25
5		20	**4e**	97
6		120	**4f**	67

Table 6 (continued)

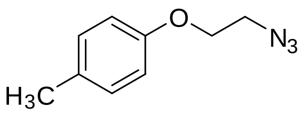
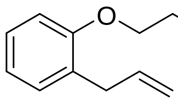
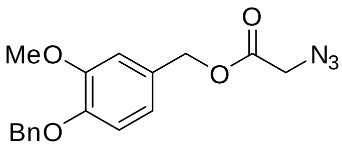
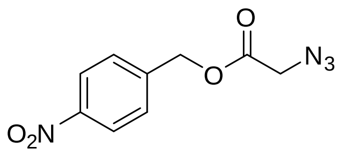
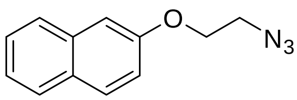
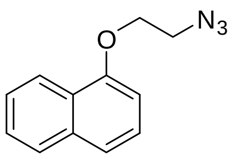
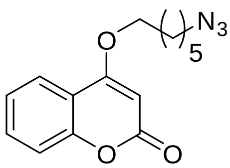
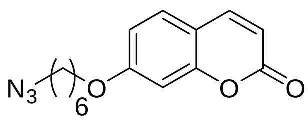
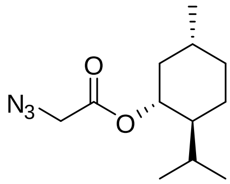
Entry	Azide	Time (min)	Product	Yield (%)
7		45	**4g**	88
8		120	**4h**	98
9		30	**4i**	29
10		20	**4j**	27
11		20	**4k**	53
12		60	**4l**	70
13		120	**4m**	84
14		60	**4n**	41

Table 6 (continued)

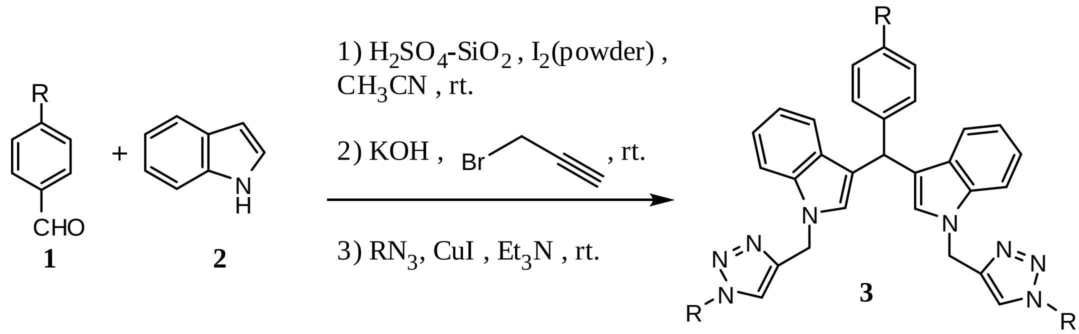
Entry	Azide	Time (min)	Product	Yield (%)
15		120	**4e**	92

In the first part of project, we synthesized 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) **3** in one pot two steps of Friedel-Craft alkylation and propargylation for using as precursor in the click reaction. Then the desired product 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**s 4** were prepared *via* 1,3-dipolar cycloaddition click reaction by carrying out the reaction of bisindole **3** with a variety of azides to obtain bisindole triazoles fifteen analogues.

Part 2 Synthesis of 3,3'-(4-chlorophenylmethylene)-bis-(1-(prop-2-ynyl)-1*H*-indole)triazole derivatives *via* one-pot 3 steps Friedel-Craft alkylation, propargylation and click reaction.

To investigate the condition for one pot synthesis of bisindole-triazole, we screened the reaction condition using our previous study. The conditions were optimized by performing of various benzaldehyde (1 equiv.) **1** and indole **2** (2.2 equiv.) using I_2 powder (0.03 mmol) and H_2SO_4-SiO_2 (0.0120g) as a catalyst in first step, KOH (1.90 mmol) as a base and propargyl bromide (2.2 equiv.) in second step, (azidomethyl)benzene (2.2 equiv.) and CuI (25%mol) as catalysts in final step. This reaction was studied as a model reaction in different condition. The results are listed in Table 1.

Table 1 Synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1*H*-indole) triazole *via* one-pot 3 step by carrying out the reaction using a variety of benzaldehyde



Entry	R_1	Time (hr.) Step 1	Step 2	Step3	Product	Yield (%)
1	Cl	1	2.5	1	**3a**	72
2	Cl	1	2.5	1	**3a**	62[a]
3	F	1.5	4	15	**4a**	-
4	NO_2	1	2	0.5	**5a**	46
5	$N(CH_3)_2$	26	4	0.5	**6a**	66

[a] was filtered to remove the precipitate

As shown in Table 1, the optimum reaction conditions were found when 4-chlorobenzaldehyde was used as starting material to perform one pot reaction at room temperature (Table 1, Entry 1). This condition was used in the synthesis of 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1*H*-indole) triazolederivetive*via* one-pot 3 steps using various azide derivatives.

Synthesis of 3,3’- (4-chlorophenylmethylene)bis(1-(prop-2-ynyl)-1*H*-indole) triazole*via* one-pot 3 steps using various azide derivatives.

With the optimized reaction condition in hand, we investigated the generality of this reaction by carrying out the reaction using various azide derivatives. As shown in Table 2, a wide range of azides gave the desired synthesis of 3,3’-(4-chlorophenylmethylene)bis(1-(prop-2-ynyl)-1*H*-indole) triazole **3a-3n** in low to good yields.

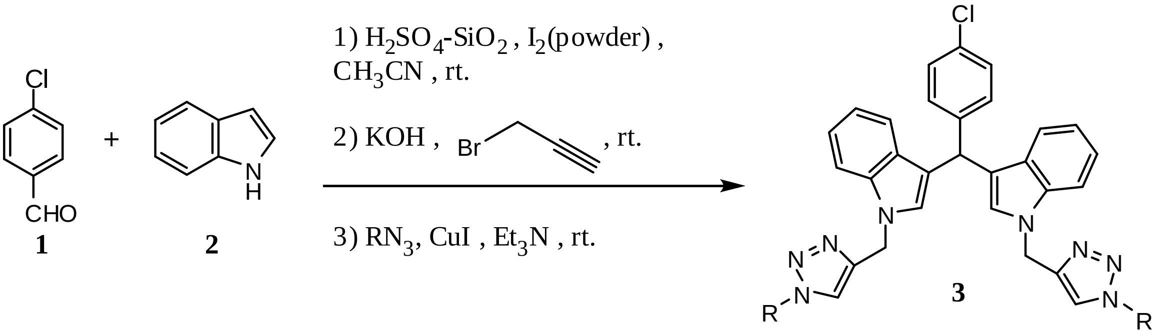
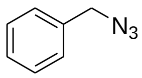
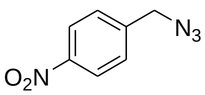
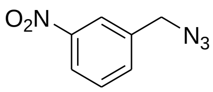
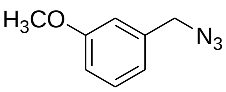
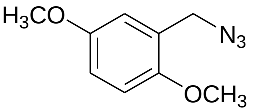
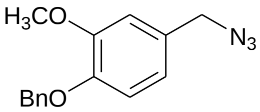
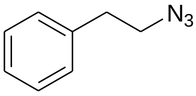
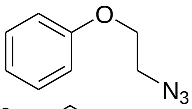
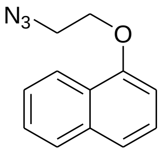
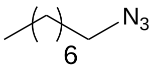
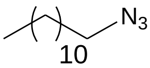
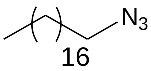
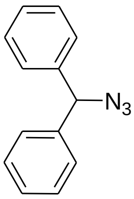
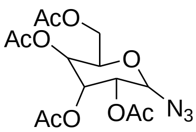


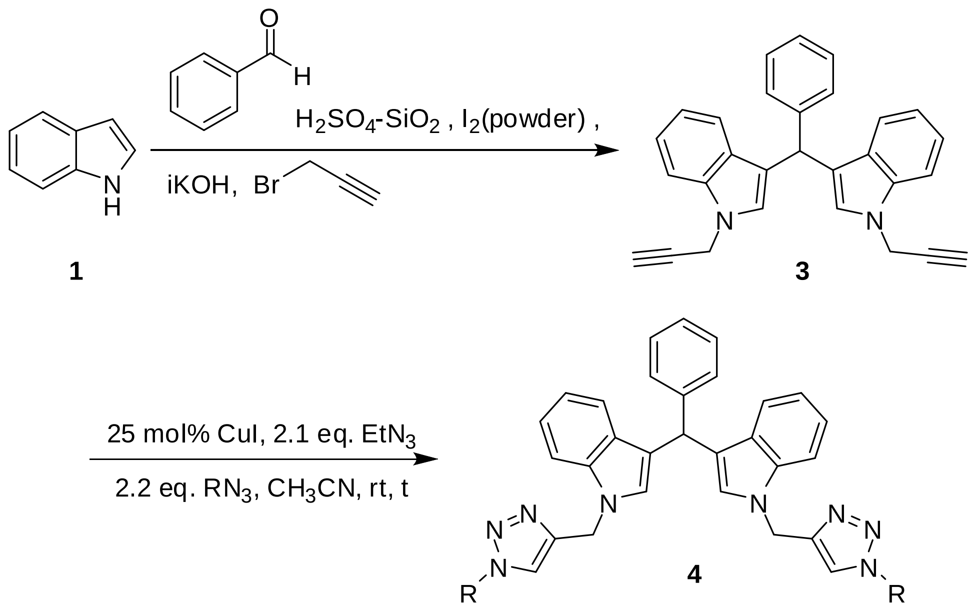
Table 2 Synthesis of 3,3’- (4-chlorophenylmethylene)bis(1-(prop-2-ynyl)-1*H*-indole) triazole*via* one-pot 3 steps using various azide derivatives.

Entry	Azide	Time (h)	Product	Yield(%)
1		1	**3a**	72
2		1	**3b**	60
3		1	**3c**	24
4		1	**3d**	39

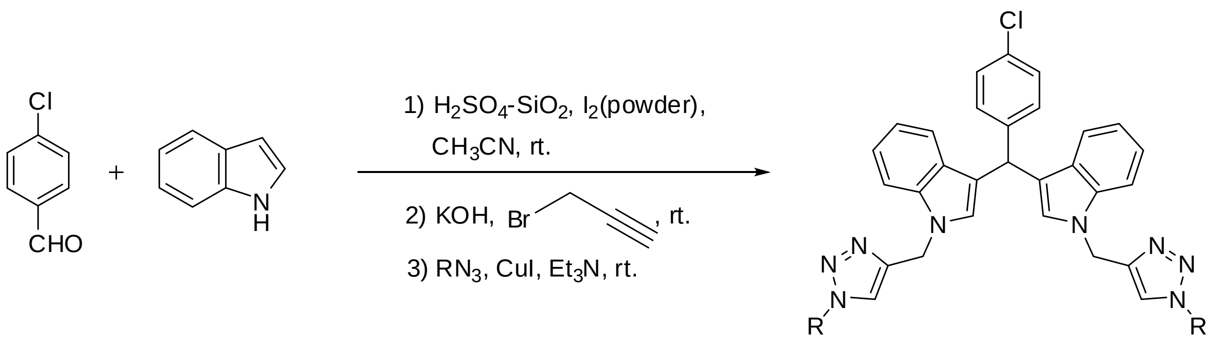
Entry	Azide	Time (h)	Product	Yield(%)
5		1	**3e**	21
6		1	**3f**	62
7		1	**3g**	35
8		1	**3h**	48
9		1	**3i**	34
10		1	**3j**	12
11		1	**3k**	27
12		1	**3l**	66
13		1	**3m**	72
14		1	**3n**	73

Chapter 3: Conclusion

In this work, we synthesized two types of bisindole triazoles. In the first part, we studied and investigated the best conditions for each step of Friedel-Craft alkylation, N-propargylation and click reaction. fifteen analogues of desired product 3,3'-(phenylmethylene)bis(1-(prop-2-ynyl)-1H-indole) triazole**s 4** were prepared in fair to good yields.



In the second part, the synthesis of 3,3’-(4-chlorophenylmethylene)-bis-(1-(prop-2-ynyl)-1*H*-indole)triazole derivatives were carried out *via* one-pot 3 steps Friedel-Craft alkylation, propargylation and click reaction. In first step, I_2 powder and H_2SO_4-SiO_2 were employed as catalysts in the presence of CH_3CN as a solvent. In second step, KOH was employed as base in solution of CH_3CN. The final step, the click reaction was performed by using CuI and Et_3N as catalyst in CH_3CN as solvent. Fourteen examples were obtained in fair to excellent yields (17-99%) using this procedure.



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Output / Outcome

ผลงานที่จะตีพิมพ์ในวารสารวิชาการนานาชาติ อยู่ระหว่างการดำเนินการ จำนวน 1 เรื่อง

Saelim, N., Kasemsook, T., Sirion, U., Saeeng, R. One pot synthesis of bisindole triazole, manuscript in preparation.

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   นายธีรชาติ เนียมรอด