Adamantylated Ligands for Supramolecular Systems Bearing a Carboxylic Moiety

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Zásady pro vypracování:

I. Teoretická část

1. **Přehled supramolekulárních systémů cucurbit[n]urilů a cyklodextrinů s vysoce afinitními ligandy.**
2. **Přehled pH-responsivních systémů na bázi výše uvedených kavitandů.**

II. Experimentální část

1. **Prověření možností syntézy titulních ligandů.**
2. **Syntéza titulních ligandů v dostatečném množství a kvalitě.**
3. **Provedení a vyhodnocení fyzikálně-chemických charakterizačních experimentů (MS, NMR, ITC).**

Rozsah diplomové práce:

Rozsah příloh:

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[1] P. D. Beer, P. A. Gale, D. K. Smith. Supramoelcular Chemistry. Oxford, 1999. ISBN 0-19-850447-0.

[2] J. W. Steed, J. L. Atwood. Supramolecular Chemistry. Chichester, 2000. ISBN 0-471-98791-3.

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[5] J.-M. Lehn. Supramolecular Chemistry: Concepts and Perspectives. Weinheim. ISBN 3-527-29311-6.

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ABSTRAKT

Hlavním cílem tohoto výzkumu byla příprava ditopických ligandů pro supramolekulární systémy, které nesou v molekule dvě adamantanová vazebná místa a karboxylovou skupinu. Klíčovým intermediátem byl symetricky substituovaný 1,2-bis{4-[(1-adamantyl)karbonyl]fenyl}acetylen. Jako výchozí látka pro přípravu tohoto derivátu byla vybrána adamantan-1-karboxylová kyselina, která byla po převedení na příslušný acylchlorid nechána reagovat s 4-methylfenylmagnesium bromidem. Vzniklý keton byl radikálově bromován a následně převeden na odpovídající fosfoniovou sůl. Paralelně byl připraven příslušný aldehyd a Wittigovou reakcí byl následně získán příslušný alken, který byl sledem bromace a dehydrobromace převeden na klíčový acetylenový meziprodukt. Poté byla studovaná 1,3-dipolární cykloadiční reakce za účelem přípravy 1,4,5- a 2,4,5-trisubstituovaných 1,2,3-triazolů. Každá modelová reakce byla provedena za přítomnosti CuI jako katalyzátoru. Dále byla studována možnost přípravy cyklopropenových derivátů reakcí acetylenového intermediátu s ethyl-diazoacetátem.

Klíčová slova: adamantan, 1,2,3-triazol, cyklopropen, cykloadice, Wittigova reakce.

ABSTRACT

Preparation of ditopic ligands for supramolecular systems, which bear two adamantane and one carboxylic group, was the main goal of this work. Key intermediate was symmetrically substituted 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne. As starting compound for preparation of the key intermediate, adamantane 1 carboxylic acid was used. This acid was initially transformed to adamantane-1-carbonyl chloride and subsequently reacted with 4-methyl-1-bromotoluene to give corresponding ketone. The ketone was brominated under radical conditions, and then transformed to phosphonium salt. Separately prepared aldehyde was transformed by Wittig reaction to produce symmetric alkene, which was brominated and subsequently dehydrobrominated to give desired key alkyne. After this, 1,3-diploar cycloaddition reactions were studied with aim to prepare 1,4,5- and 2,4,5-trisubstituted 1,2,3-triazoles. Each model reaction was performed in presence of CuI as a catalyst. Later, preparation of cyclopropane derivatives by reaction of alkyne intermediate and ethyl diazoacetate was studied.

Keywords: adamantane, 1,2,3-triazole, cyklopropene, cycloadition, Wittig reaction

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CONTENTS

INTRODUCTION

General properties of 1,2,3-triazoles

In last ten years, number of articles, which are related to different substituted triazoles increased exponentially. Year by year, there is tremendous improvement when we talk about differently substituted 1,2,3- triazoles or rather we talk about synthesis or understanding of mechanism of 1,2,3-triazole formation.

Scientists cannot stop to be impressed with such huge scope of fields in that differently substituted triazoles could be applied and show their efficiency. Particularly, efficiency it is not allied just to high yield and speed of reaction, but also to biological activity, stability, and flexibility to apply 1,2,3-triazoles in any branch of scientific research from nanomaterials and supramolecular chemistry to medicine. However, nowadays, many strategies has been used to synthetize new differently substituted 1,2,3-triazoles that shows biological activity. This became obvious by a number of scientific publications in recent years.

The 1,2,3-triazole is a heterocyclic compound with three nitrogen atoms within the ring. Preparation reactions of 1,2,3-triazole heterocyclic system have been known since the 19th centrury. The triazole ring can also contain another heteroatom (for example sulphur or oxygen). A typical example of this group is the 1,2,3-triazole, also called v-triazole, „v" means a vicinal arrangement of N-atoms (for structure, see Figure 1).

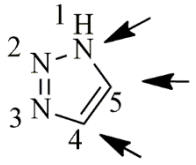


Figure 1. Structure of 1,2,3-triazole. Positions available for substitution are indicated by arrows.

Despite that triazole compounds are known for more than 100 years, no 1,2,3-triazole has been isolated from any natural materials.[1–4]

Integration of the triazole ring into the structure of other compounds has an effect on increasing the thermal stability and reducing their sensitivity. Triazoles are considered to be

highly stable aromatic compounds due to their resistance to acid and basic hydrolysis and reductive and oxidative conditions.[5]

The relative stability of triazole ring allows to form different structures with various substituents. 1,2,3-triazole as a heterocycle has a high dipole moment about 5 D and it could also take part in hydrogen bond formation as well as in dipole–dipole and π···π stacking interactions.[6]

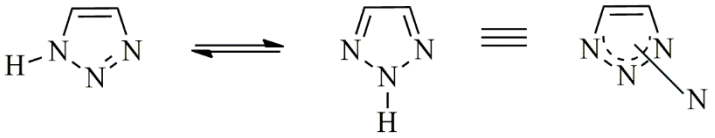


Figure 2. Tautomer forms of the 1,2,3-triazole

In dilute solution and at room temperature, it is characteristic that the 1H and 2H tautomers of 1,2,3-triazole appear at equilibrium. In the case of more concentrated solutions and at lower temperatures, the molecules in 1H-forms are associated via intermolecular H-bonds.

Furthermore, during the late sixties and early seventies of the 20th century, scientists researched on molecular orbital calculation of both tautomers (1H and 2H) of the 1,2,3-triazole. Physical properties, including bond lengths, resonance energy, electron densities and dipole moments showed that 2H structure is slightly more stable than 1H tautomers. Nevertheless, in the case that a proton is replaced by any bigger group, that will stay fixed and no group shift will occur.[7]

Acid-base properties of 1,2,3-triazoles

The 1,2,3-triazole is a weak base. The pK_b of 1,2,3-triazole is 1.17 that makes this triazole to be less basic than pyrazole. On the other hand, the unsubstituted nitrogen triazole atom can release a proton to act as an NH-acid. The acidity of 1,2,3-triazole is characterized with a pK_a value of 9.3.[7]

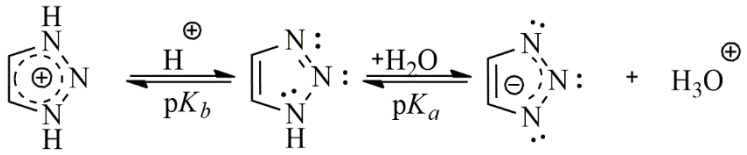


Figure 3. Acid-base behavior of the 1,2,3-triazole

I. THEORY

1 SYNTHETIC STRATEGIES

1.1 Introduction

Broad number of synthetic methods for preparation of 1,2,3-triazoles is possible to classify into four sections, according to the method used to form each particular bond, namely, the N(1)-N(2), C(5) N(1)[or C(4)-N(3)], C(5)-N(1) and C(4)-N(3) bonds; and the C(4)-C(5) and N(1)-N(2)bonds, as is depicted in Figure 4.[8]

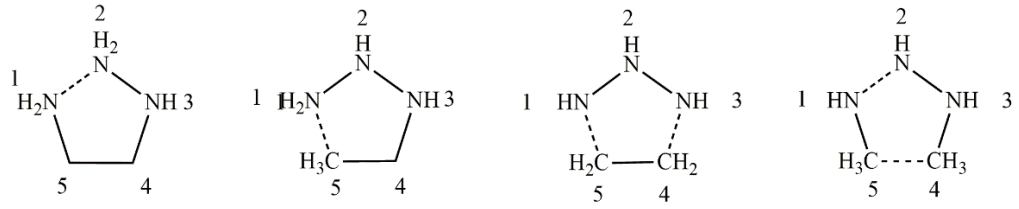
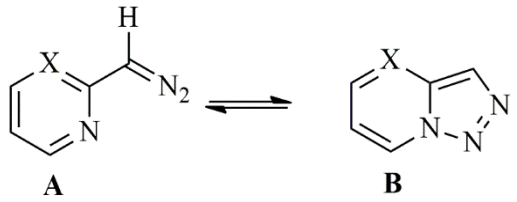


Figure 4. Synthetic methods of 1,2,3-triazole

Synthesis of triazoles had a few milestones through their history beginning they were first time prepared by von Pechmann (1888). Each of those milestones steadfastly follow number of prepared compounds based on 1,2,3-triazole. Besides von Pechmann, there are two more important scientists who significantly changed point of view on 1,2,3-triazoles. That are Luis Pauling (1933) who for the first time discovered "Click chemistry", and later Sharpless (2001) who explained the mechanism of "Click" reaction towards triazoles.

1.2 Thermal rearrangements and transformations of 1,2,3-triazoles

1,2,3-triazole is unique structure because of chemical and physical properties which give the ability to make various rearrangements within the molecule. This feature is essential for unique synthetic methods and gives a lot of space for the fundamental studies of unusual reactions. Those rearrangements are controlled by three factors. The first factor is an existence of an equilibrium between 1,2,3-triazole and α-diazoiminese. The second factor appears in capacity of both imino- and diazo groups to cyclize onto electrophilic and nucleophilic functionalities. And finally third, there is an effortless break of N1—N2 bond. L'abbé was the first one who classified all possible rearrangements of five-membered heterocyclic compounds depending on participation of side-chain atoms.



X=CH ($\Delta\Delta G = -2.6$ kcal/mol) X=N ($\Delta\Delta G = -(16–18)$ kcal/mol)

$$\Delta\Delta G = \Delta G_A - \Delta G_B$$

Figure 5. Relative stabilities of diazoimine and triazole forms in hterocyclic systems

1.2.1 Dimroth Type Rearrangements

For the first time the term „Dimroth rearrangement'' was introduced in 1963 for the isomerisation of 1-subtituted 1,2,3-triazole of type A (Figure 6) to 5-amino substituted 1,2,3-triazole C with corresponding diazo acetamidines B as an ring-opened intermediate. Later subsequent recyclization is followed by amidine tautomerization to a nitrogen atom of the former amino group attached to the ring to provide final product (Figure 6). O. Dimorth for the first time proved this rearrangement on 5-amino-1,2,3-triazole to 5-anilino-1,2,3-triazole.

In the basic solvent, the acid form C is preferred and therefore the higher ratio of C/A can be determined in the equilibrium mixture.

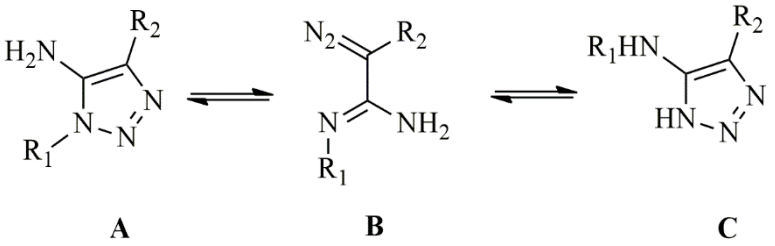


Figure 6. Dimroth rearrangement of 1,2,3-triazoles

1.2.2 Cornforth-type rearrangements

This type of 1,2,3-triazole rearrangement can be demonstrated on molecule A (Figure 7), which bears a C=N, N=N, or C=S functionalized substituent at position 4 to lead to isomeric triazoles or thiaidiazoles, respectively C. Figure 7 presents competitive cyclization of the intermediate diazo function of compound B to the nitrogen atom of both imino groups,

including two atoms of the 4-substituents. Cornforth rearrangement take place for different R groups including hydroxyl, amino, alkyl, aryl.

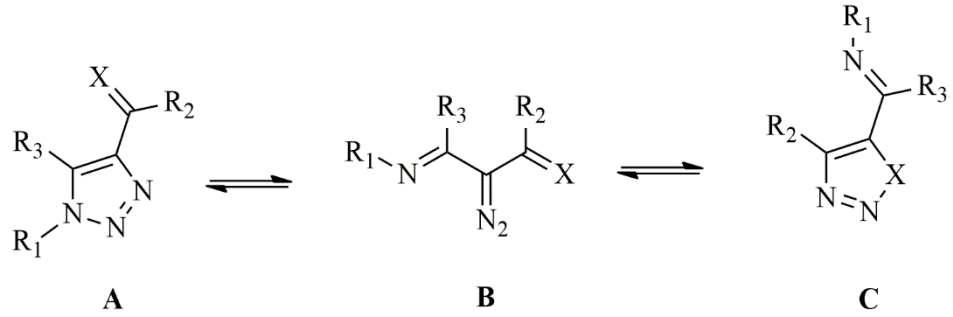


Figure 7. Rearrangement with participation of two atoms of the side chain

1.2.3 L'abbé-type rearrangements

L'abbé rearrangement is specific for triazoles bearing electron-withdrawing substituents at position 1 and 4 of the ring. This rearrangement is followed by single imino group which involve competitive 1,5-cyclizations onto two 1,3-dipole-moieties. For the first time this rearrangement was proved by L'abbé and Dehaen on 5-diazomethyl-4-ethoxycarbonyl-1,2,3-triazoles A to diazoacetates B (Figure 8).

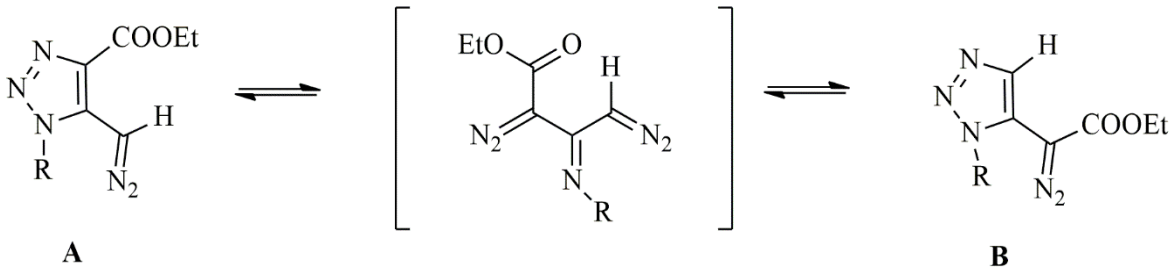


Figure 8. L'abbé rearrangement of 5-diazomethyl-1,2,3-triazoles

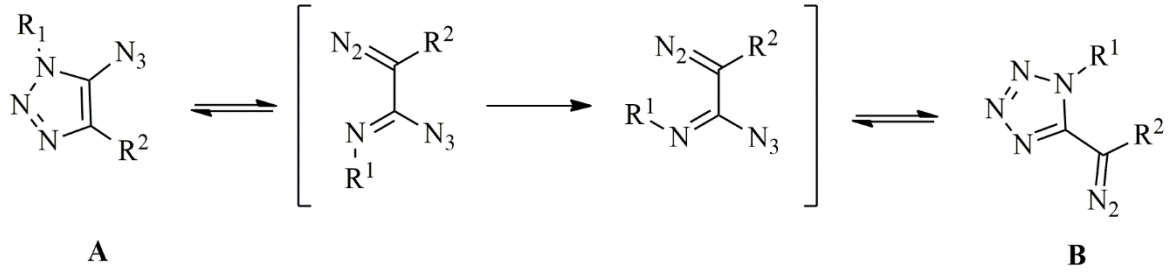


Figure 9. L'abbé rearrangements of 5-azido-1,2,3-triazoles to 5-dimethyl-tetrazoles

This mechanism has been proved on 5-azido-1,2,3-triazoles A bearing strong electron-withdrawing substituent at position 4 (cyano, aldehyde, ester group), to form 5-diazomethyl-triazoles B (Figure 9). Adding electron-withdrawing substituent at the position 1 will increase the rate of the process. Reaction time can be slightly reduced by use of non-polar solvent.

1.2.4 Tandem rearrangements

Tandem rearrangement relates to a process, in which two adjacent heterocycles are rearranged. Figure 10 shows an example of Tandem rearrangement that could work for both molecules 1,2,3-triazole and 1,2,3-thiadiazole. Rearrangement is carried on in three steps. First, the hydroxytriazole A ring opens to form diazoamides B. Subsequently, B rearranges to isomeric diazo compound C known as L'abbé-type rearrangement and in the final step isomeric hydroxyl triazole D is created by ring closing.

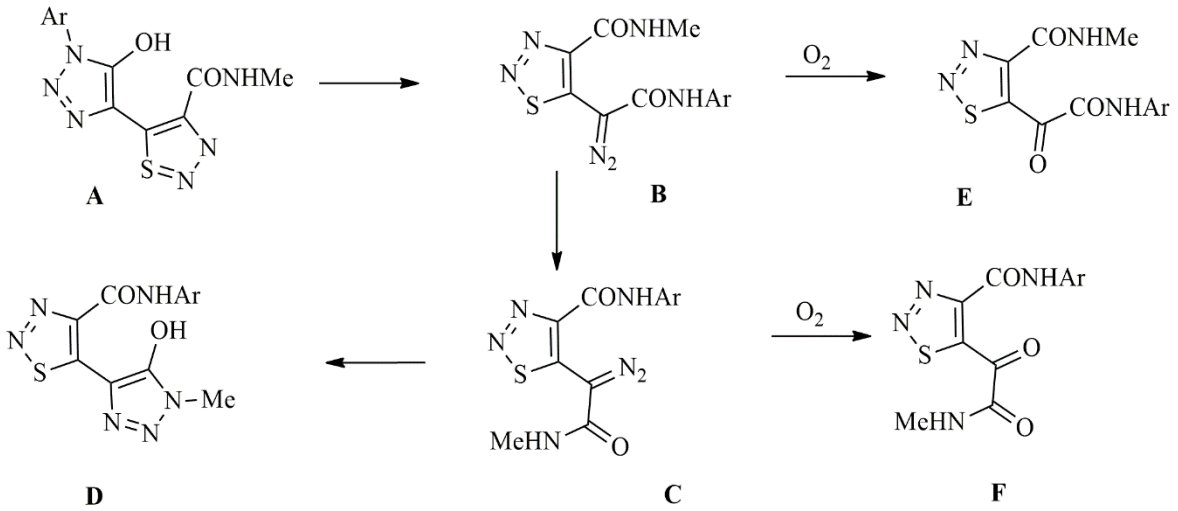


Figure 10. Tandem rearrangement of thiadiazolyltriazoles A to thiadiazolyltriazoles D

1.2.5 Thermolysis of 1,2,3-triazoles

As it was mentioned earlier, 1,2,3-triazoles can form highly stable structures due to their aromaticity. This is the reason why it is necessary to reach high temperature for the elimination of dinitrogen. Figure 11. shows possible products presented as carbine F, diradical E, and zwitterion F, that can be formed from 1,2,3-triazole in reaction under high temperature.

Structures E–G are stabilized if initial triazole bears aromatic substituents. In the case of strongly electron withdrawing substituent activation energy will be lowered for the elimination of dinitrogen. By presumption that substituent in position N1 is able to react intramolecularly with radicals by this way, a lot of different compounds including heterocyclic systems can arise in the mixture.

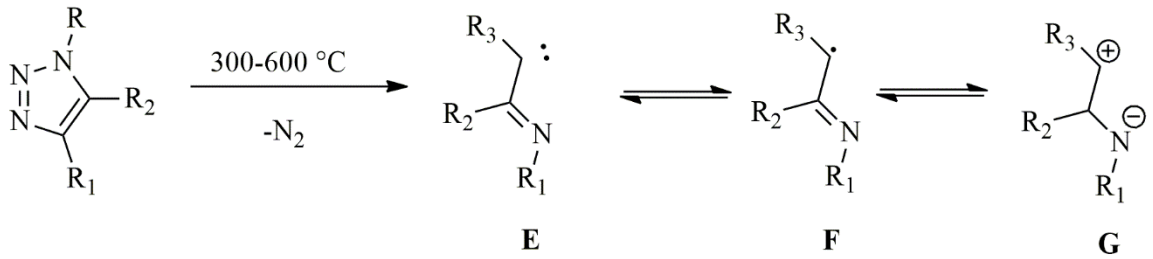


Figure 11. Resonance form E, F, G of species formed in pyrolysis of 1,2,3-triazoles at 300–600 °C

Thermolysis of 1-aryl-1,2,3-triazoles was described by passing through singlet form E followed by Wolff rearrangement and ring closing to form indoles H (Figure 12).[9]

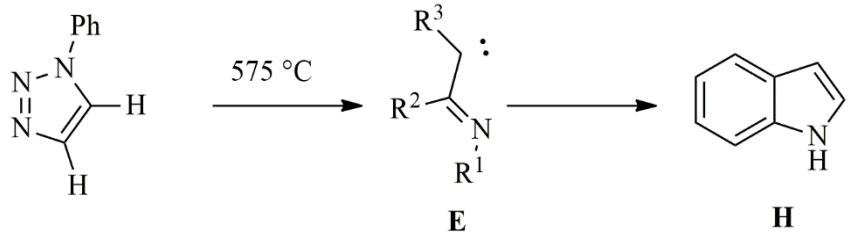


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Figure 12. Thermal transformation of 1-phenyl-1,2,3-triazole to indole

1.3 Click chemistry

„Click chemistry" was discovered for the first time by Linus Pauling in 1933[10]. But the first scientist who described mechanism of "click chemistry" was K. B. Sharpless in 2001. Basic principle of "click chemistry" method is to generate substances quickly and reliably by joining smaller units together. Actually, "click chemistry" does not present some specific reaction, it is rather a concept which mimics nature. Utilizing of "click chemistry", it is easy to achieve desired products in very high yields mostly without by products or with very small yields of by-products. This powerful method has demonstrated to work properly under several conditions. Moreover, click chemistry stands for philosophy of compound preparation that include wide spectrum of reactions with dissimilar reaction mechanisms but similar reaction trajectories.

Organic azides and terminal alkynes are transformed by the copper-catalyzed reaction into 1,4-disubstituted-1,2,3-triazoles. Catalyzed reaction transforms terminal alkynes and organic azides completely into 1,4-disubstituted 1,2,3-triazoles. In contrary, uncatalyzed reaction needs higher temperature to provide mixtures of 1,4- and 1,5-triazole regioisomers.[10] Before the discovery of copper catalyzed reactions, later known as CuAAC, it had been published more than 7000 1,4-disubstituted 1-*H*-1,2,3-triazole compounds.[10] "Click chemistry" had been described by a set of tight criteria. In the year 2008, more than 600 papers were published and more than 10 000 citations associated with term "click chemistry". It can be compared with data from the year 2005, i.e, 100 papers and 1 000 citations, to demonstrate a substantial increase of interest. More than 14 % of all publications till 2008 are related to drug discovery while up to two-thirds of publication relates to broad science categories like biotechnology and materials.[11]

Synthesis of 1,2,3-triazole must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions, readily available starting materials and reagents, the use of no solvents or a solvent that is benign (such as water) or easily removed, and simple product isolation. High thermodynamic driving force (>20 kcal/mol) is the force which drive click reaction. This driving force is generally allied with the formation of carbon-heteroatom bonds.[12]

1.2 1,3-Dipolar cycloaddition

One of the most common and known way for the synthesis of the 1,2,3-triazole ring is the 1,3-dipolar cycloaddition with hydrazoic acid or organic azides which react with alkynes. This process is depicted in Figure 13.

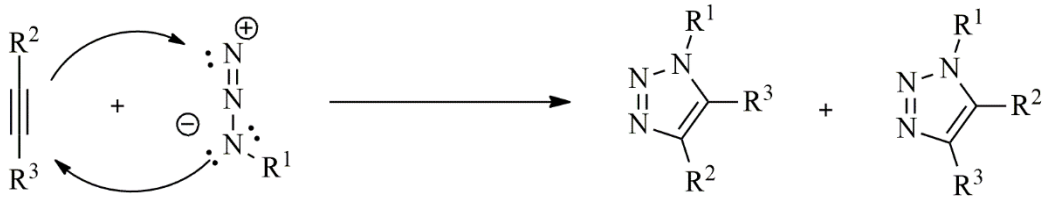


Figure 13. 1,3-Dipolar cycloaddition toward the triazole ring

The 1,3-dipolar cycloadittion is similar to Diels-Alder reaction. Both these groups belong to pericyclic reactions. Pericyclic reactions are considerable for the synthesis of heterocycles and/or conversions to new cyclic structures. The main similarity between 1,3-dipolar cycloaddition and Diels-Alder reaction is that both pass through a cyclic transition state including 6 electrons (i.e., 4π + 2n or 6π, respectively). The dissimilarity lays in that three atoms supply the four electron in the case of 1,3-dipolar cycloadditions instead of four atoms in a Diels-Alder reaction and thus 1,3-dipolar cycloadition leads to 5-memberd ring. 1,3-dipolar cycloaddition same as wide range of cycloaddition reactions are followed with high sterocontrol.[13]

The evolution of the 1,3-dipolar cycloaddition started 100 years ago. During these one hundred years, different 1,3-dipoles have been discovered. Several scientists tried to describe the mechanism of the 1,3-dipolar cycloaddition, but Husigen, Woodward and Hoffman are some of the most important. By the 1960's, Husigen published an article that describes accurately the mechanism of the 1,3-dipolar cycloadittion. One of the most important features of the 1,3-dipolar cycloaddition mechanism is the control of the diastero- and enantioselectivity.

A 1,3-dipole appears as a three-atom connected structure, which can be defined as a c-b-a structure, as it is depicted in Figure 14.

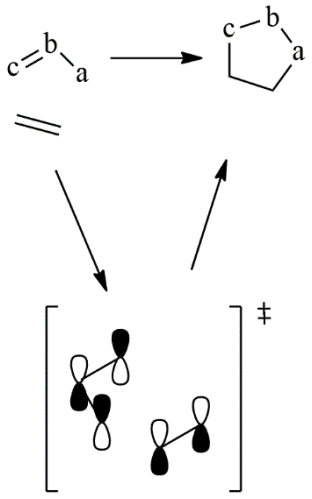


Figure 14. Description of c-b-a structure

Two groups of 1,3-dipoles can be distinguished: 1) The allyl anion type which can be typify by four electrons in three parallel p_z orbitals orthogonal to the plane of the dipole and the curved 1,3-dipole. Figure 15. shows the two resonance structures where the three centres have an electron octet, and two structures in which a or c has an electron sextet. Atom b can be represented by nitrogen, oxygen or sulfur.

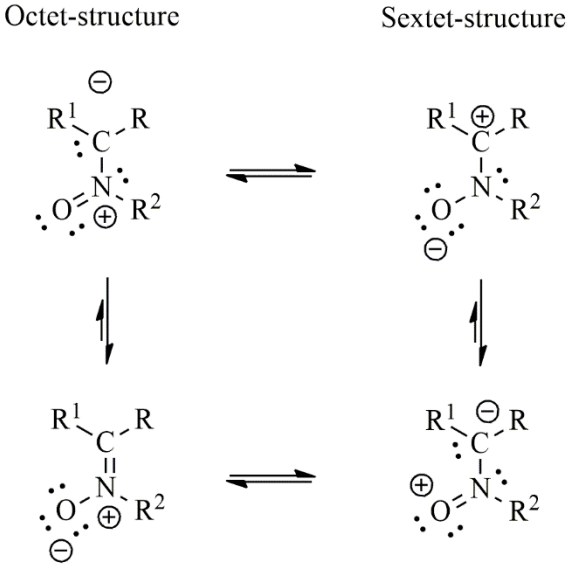


Figure 15. Allyl anion type 1,3-dipole

2) The second group is propargyl/allenyl anion type, which has an extra π orbital situated in the plane orthogonal to the allenyl anion type molecular orbital, and the former orbitals are not directly involved in the resonance structure and the reactions of the dipole.

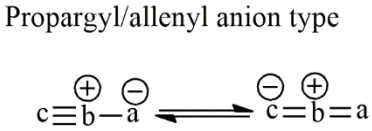


Figure 16. Propargyl/allenyl anion type of 1,3-dipole

Figure 16 presents a propargyl/allenyl anion type, but as can be seen, the form is linear. The central atom b can be nitrogen. However, the three resonance structures, which are also possible to draw, are excluded in the previous representations. The 1,3-dipoles could be demonstrated as hypervalent structures as presented in Figure 17**.**

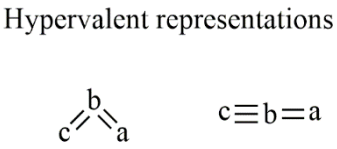


Figure 17. Hypervalent representation of 1,3-dipoles

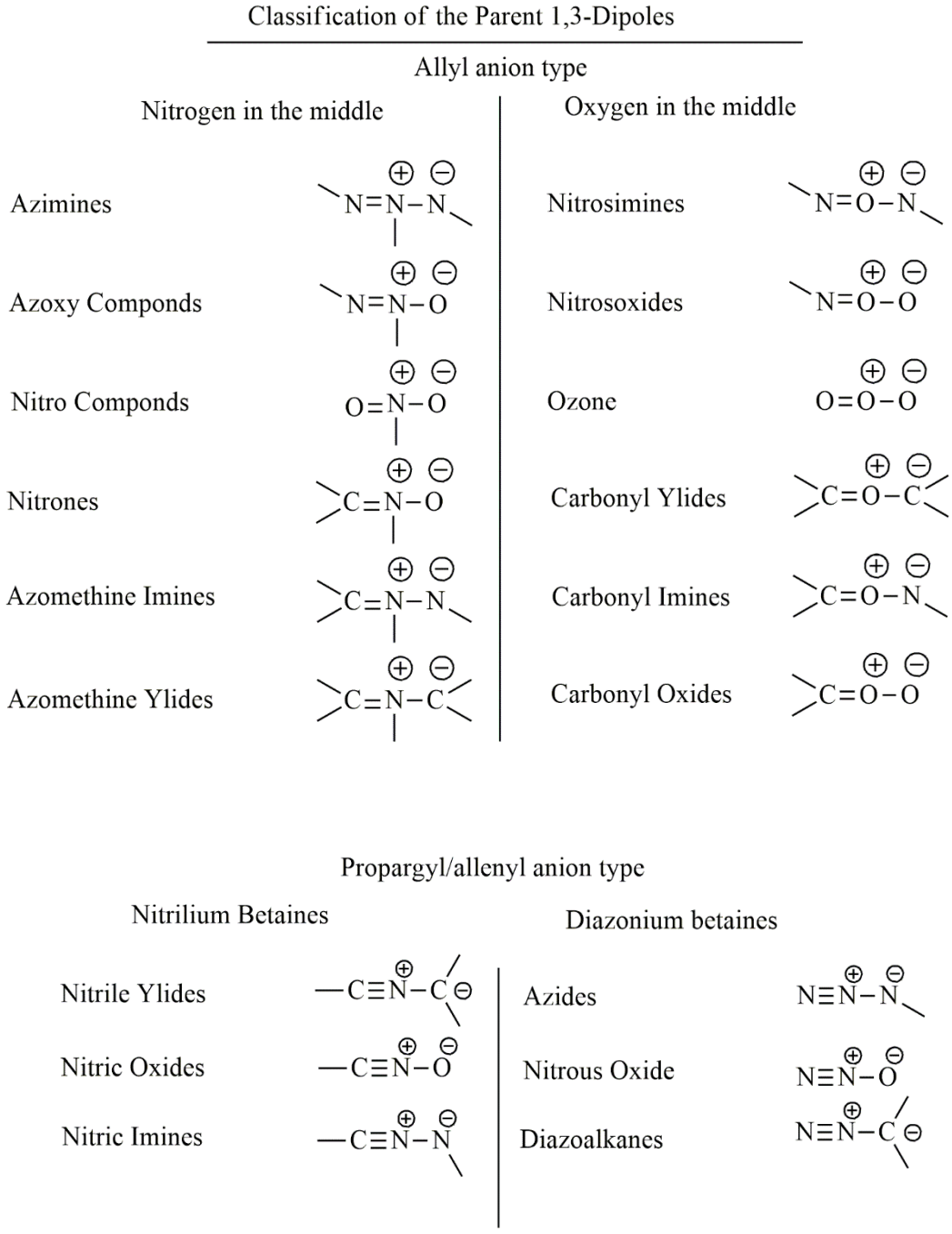
Because the 1,3-dipoles are structured from elements of the second period of periodic table of elements, and according to the literature there is a limited number of possibilities that can be formed by a change of nitrogen, carbon, and oxygen on the central atom of the dipole[14–15]. Very few articles have been published with sulphur and phosphorus containing 1,3-dipoles. The classification of two types of 1,3-dipoles are draw in Table 1.

Azide group, similarly to the alkyn functionality, is inert with molecules that are contained in the living systems cells. Additionally they can avoid protein denaturation in short time intervals, at room temperature, and in aqueous solution where pH is near to that of physiological environment. In comparing with many other reactions that uses electrophiles or nucleophiles, components of click mechanism do not react in an unwanted way within biological systems, even in the cells itself.[11]

Despite click chemistry offers so many advantages and applications, there are certain potential limitations in drug discovery that must be mentioned. Copper as one of most used catalyst could be cytotoxic and show some side effects connected with high intake of copper. High doses of copper lead to hepatitis, Alzheimer's disease as well as neurological disorder.[9]

On the other hand, azides are connected with potential toxic side effects and certain azides may have strong explosive potential.

Table 1. Classification of the parent 1,3-Dipoles



1.4 Synthesis of 2H-1,2,3-Triazoles

Introduction

3(1)H-1,2,3-triazole (formally named) was obtained as a third isomer very rarely. All regioisomers (Figure 18) are thermodynamically stable. Tautomer appears in equilibrium in solutions and have slightly different values of Gibbs energy. Content of each form can be analysed by spectral methods but it is possible to separate them from each other.

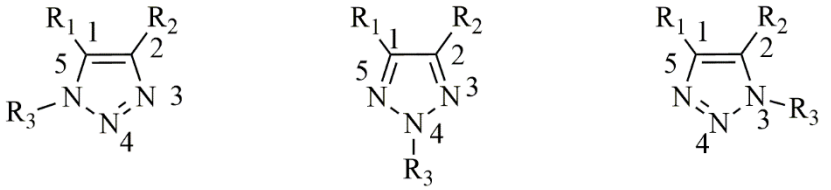


Figure 18. Triazole regioisomers

Theoretical calculations of magnetic properties of NH-1,2,3-triazoles performed at B3LYP/6-311++G(d,p) level within GIAO approach confirmed the aromatic character of these six-electron-heterocycles. Nucleus independent chemical shifts (NICS) calculated above the ring centres were −13.51 ppm for tautomer A and −13.61 ppm for tautomer B (Figure 19).[9]

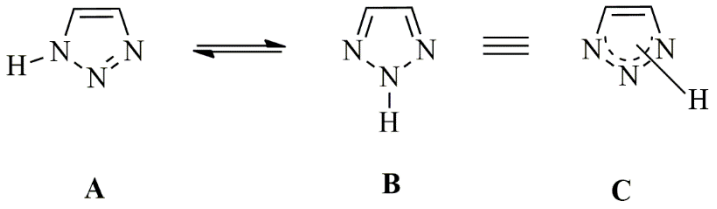


Figure 19. Molecule examples for theoretical calculation

Tautomer 1H in cooperation with tautomer 2H is more stable in solution, while the situation in gas phase is opposite (~4.0 kcal·mol^{-1}). This theoretical study was later proved by experiments[16]. N1 and N2 substituted isomers have different polarity values. The dipole moment of N2-substituted-1,2,3-triazole can be much lower than that of N1-substituted isomer (Table 2).

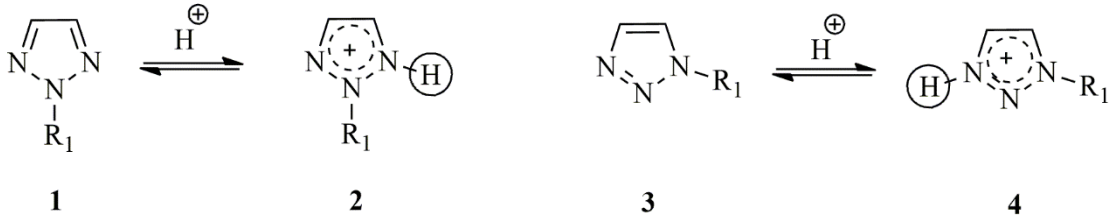


Figure 20. Acid-base behavior of 1H- and 2H-1,2,3-triazoles

1,2,3-Triazole can behave as a weak acid or weak base similar as phenol. This amphoteric nature can be demonstrated by 2-methyltriazole (1), which display much weaker basicity in comparison with 1-methyl-1,2,3-triazole(3) (Figure20).

Table 2. Polarity and acidity of 1H- and 2H-1,2,3-triazoles

No.	R^1	pK_a	μD
1	H		5.97
2	H	1.17	1.85
3	Me	<1	0.37
4	Me	1.25	4.46

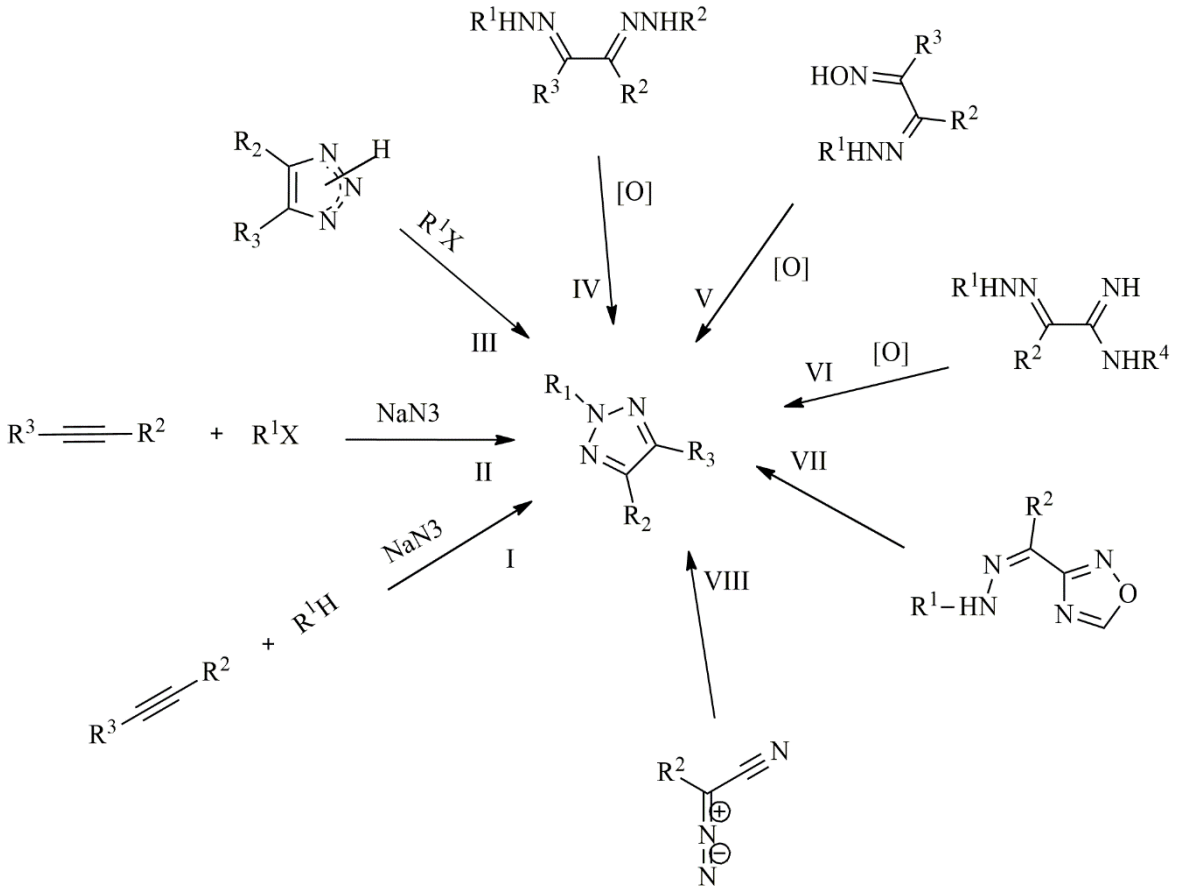


Figure 21. Methods for the synthesis of N2-substituted-1,2,3-triazoles

Figure 21. shows general methods for obtaining 2-substituted isomer of 1,2,3-triazoles. In contrary to N1-substituted isomer, there is no universal method to obtain 2-isomers, however many synthetic methods have been published. As most known method for synthesis of triazoles is cycloaddition of azides to acetylenes (I), one-pot three-component cyclization (II), reaction of 2H-1,2,3-triazoles with electrophilic agents (III), the various cyclizations of hydrazones (IV-VI), Boulton–Katritzky rearrangement of (*Z*)-3-arylhydrazones of 3-acyl-1,2,4-oxadiazoles (VII), and intra- and intermolecular cyclization of diazocompounds (VIII).

2-Alkyl and extraordinary 2-aryl substituted 1,2,3-triazoles are possible to prepare with Huisgen azide-alkyne dipolar cycloaddition followed with postalkyl(aryl)ation or done by multicomponent and solid-phase fashion. However, it is not possible to use the nucleophilic substitution for effective preparation of 2H-substituted triazoles. The explanation of this appearance is fact that the regioselectivity of N-substitution is tough to be controlled kinetically, and nitrogen in position 1 within triazole ring will become favoured nucleophilic site under reaction conditions. 1,2,3-Triazoles bearing carbamoyl, sulfonyl or acyl in

position 2 are easy to obtain by nucleophilic substitution, but because they are not long time stable their application is seldom.[9]

2 BIOLOGICAL ACTIVITY AND RECENT EXAMPLES OF 1*H*-1,2,3 AND 2*H*-1,2,3-TRIAZOLES

1,2,3-Triazoles are also known as resistant linker between two unites of pharmacophores to give a final bifunctional and innovative drug. Thus, it has become important and applicable to develop different way to construct such functional and bioactive molecules. As infection diseases caused by microorganism result with 50 000 deaths per day, synthesis of new drugs presents one of the most important research challenge for human survival.
Another important positive effect has been recorded with differently substituted 1,2,3-triazoles against tuberculosis infection caused by *Mycobacterium tuberculosis*. This infection disease has been diagnosed in one third of world population and caused 1.5 million deaths worldwide according to the World Health Organisation. In the year 2015, Mubark H. et. al. reported around 30 differently susbstituted triazoles. One compound showed not only anti-tuberculosis effect but also cytotoxic effect against three human cancer cell (lines THP-1, A549, and PANC-1.[17]

Triazoles have been proposed as aggressive pharmacophores because of their chemical features. They involved in drug-receptor interaction, while preserving superior metabolic and chemical profile. So far, number of differently 1,4-disubstuted triazoles reached hundreds of thousands. Therefore, Alberto M. et. al. created database of triazoles called ZINClick in 2013. Database is based on literature reported aizdes and alkynes that are possible to prepare in three steps from commercially available chemicals. Inside ZINClick database is possible to find over 16 million novel, new and easily synthesizable 1,4-disubstuted-1,2,3-triazoles. ZINClick offers structures in 3D multi-conformer format up to 500 Da, with option to choose different subsets like is drug-like, lead-like, fragment-like. Purpose of ZINClick novel database is to motivate drug researchers, and offer easy access for medical and computational chemists to find their biological targets.[18]

Therefore, it is necessary to define basic synthetic strategies for preparation of 1,2,3-triazole based bioactive compounds. The best known and frequently used catalyst systems in click chemistry are based on Cu^{II} salts like copper sulfate pentahydrate or copper acetate, followed by reducing agents like sodium ascorbate. Besides Cu^{II} salts, copper(I) salts are characterized as highly effective catalytic species.

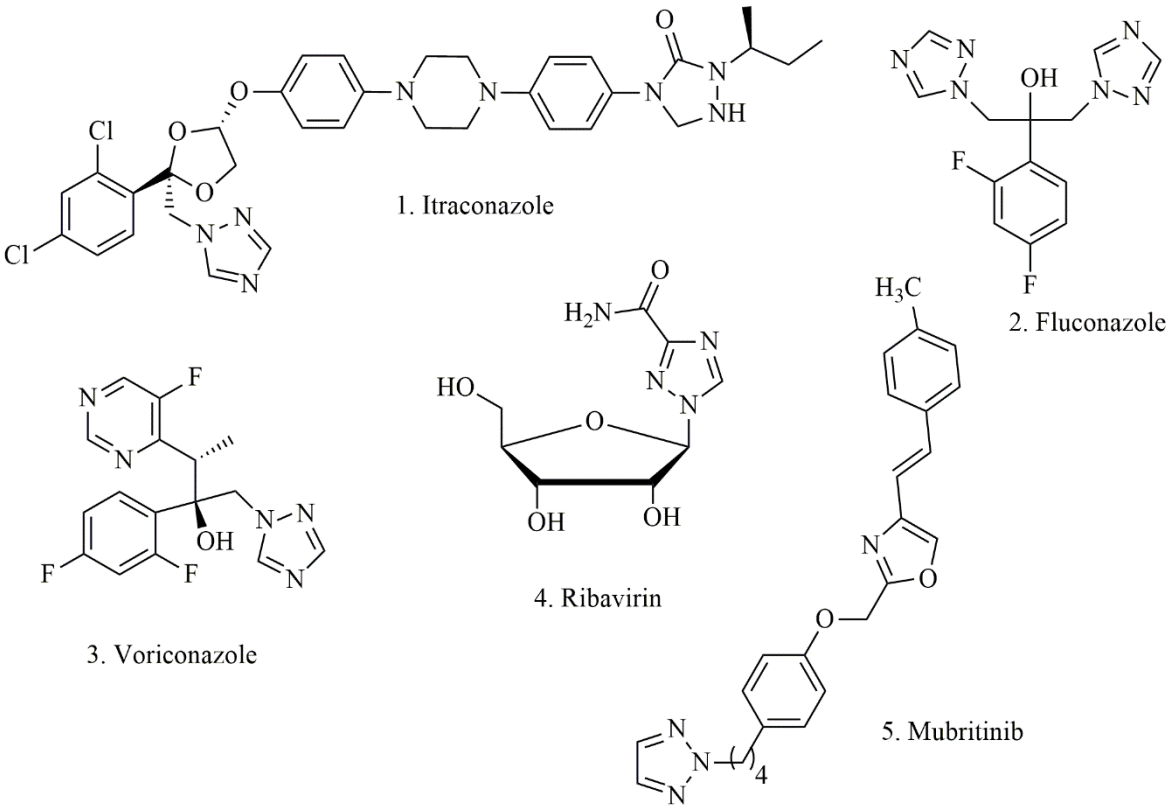


Figure 22. Antifungal drugs heaving triazole rings

Beside some very good applications like organocatalysis and applications in ionic mixtures, 1,2,3-triazoles show biological activity in wide range of diseases. Antimicrobial, antitubercular, anti-inflammatory, antiplatelet, antitumoral, and antiviral activity are some examples of the positive biological effect of triazoles. In addition, some positive results were published on treatment of several neglected diseases. Such a good result opened door of pharmaceutical market for 1,2,3-triazoles. Some antifungal examples of differently substituted 1,2,3-triazole are showed in Figure 22.

In present time, four 1H-isomers are under investigation on clinical trials, with aim to reach pharmaceutical market, and pharmacies in next few years. Figure 23 presents four 1,2,3-triazoles on clinical investigation.

Another reason, why triazoles started to be interested in pharmaceutical industry, is ability to prepare them by 1,3-dipolar cycloaddition. This cycloaddition is characterized as a highly atom-economic and effective coupling reaction in complex macrocycles synthesis. However, there are many other reasons for their application as a bioactive compound like is bioisostere.

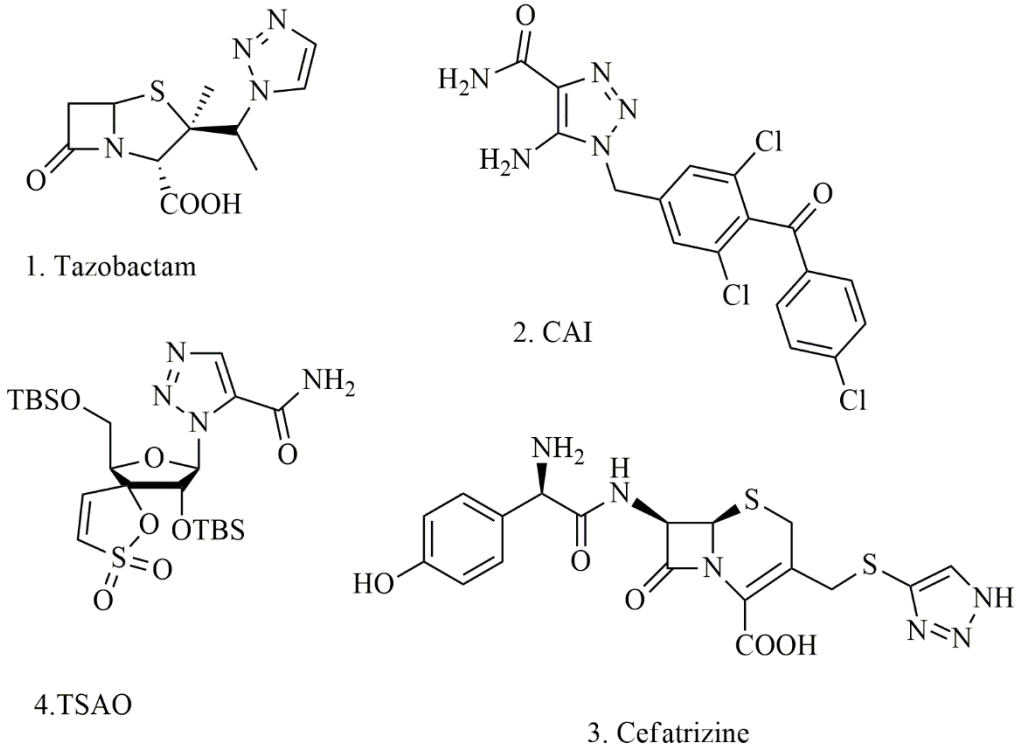


Figure 23. Four triazoles currently under clinical trials

Triazole is bioisostere of amide group, because such moieties have similar H-acceptor capacity, similar distance between substitutents (3.8–3.9 Å for amides and 5.0–5.1 Å for triazoles), as well as similar dipolar character (amide 4 Debye; trazole 5 Debye). Such properties of 1,2,3-triazoles, like ability to make hydrogen bond or participate with dipole, can lead them to biomolecular targets and improve their solubility. Nevertheless, 2H-1,2,3-triazoles have also biological activity such as antitubercular, antiarrhythmic, and aesthetic (Figure 24). Two aspect about bioactive triazoles should be mentioned. Firstly, long chain substituted triazoles display increased lipophilicity, thus enhanced permeation through cell membrane and enhanced inhibitor activity. Secondly, triazoles linked to another heterocycles and carbohydrates can increase number of hydrogen bonds and also number of interactions with bio-glyco-conjugates on the microorganism surface. [9]

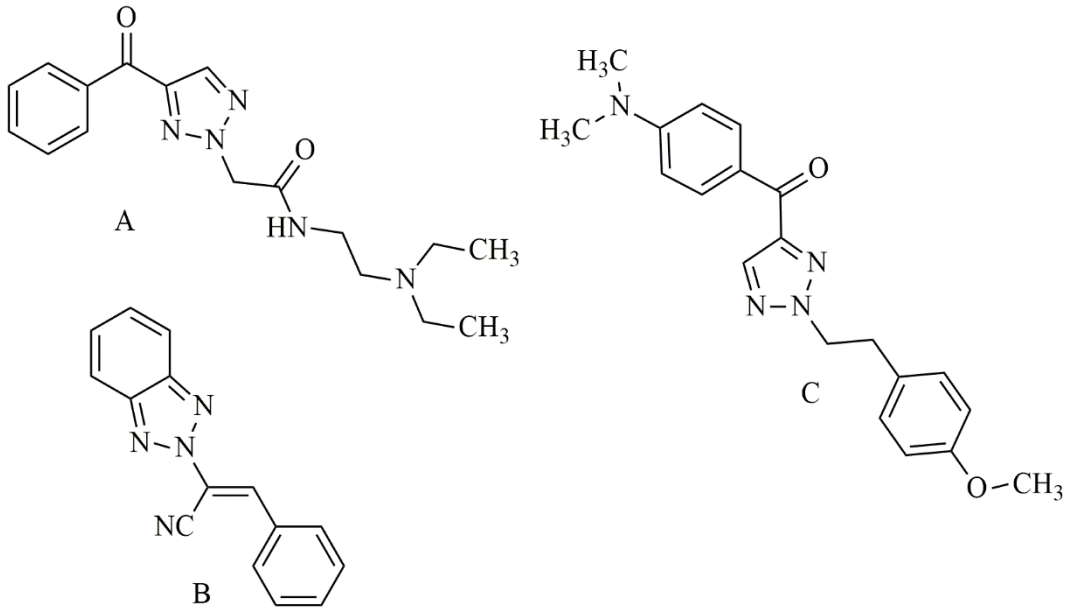


Figure 24.Triazoles with anesthetic (A), antiarrhytmic (B), antitubercular (C) activity

2.1 Continuous flow

According to the recent publications, continuous flow approach is one of the most efficient way for large scale synthesis of 1,2,3-triazoles. Such method, used to synthetize differently substituted triazoles, brings many advantages in compare to traditional batch-based approaches. Shorter reaction times, operation simplicity, excellent mass and heat transfer, efficient mixing quality are some of the most important advantages. Moreover, continuous flow is characteristic with simple and rapid scale-up and automation of chemical processes. Because of all abovementioned benefits, continuous flow technique has powerful influence on modern synthetic chemistry in the range from laboratory to industrial scale experiments or preparation.

1,3-Dipolar cycloadditions are catalyzed by copper(I) powder as it is one of the cheapest and fastest accessing catalysts for this type of reaction. This was the reason to choose it for continuous flow technique as well. Initially, high reaction yields were achieved by high pressure and temperature. Later, the temperature was lowered to the room temperature and a reactions were performed with both acid and base additives to advance the safety of synthesis using unstable azides. Potential precursors for drugs based on 1,2,3-triazole-substituted β-aminocy-clohexanecarboxylates were target molecules in this study.

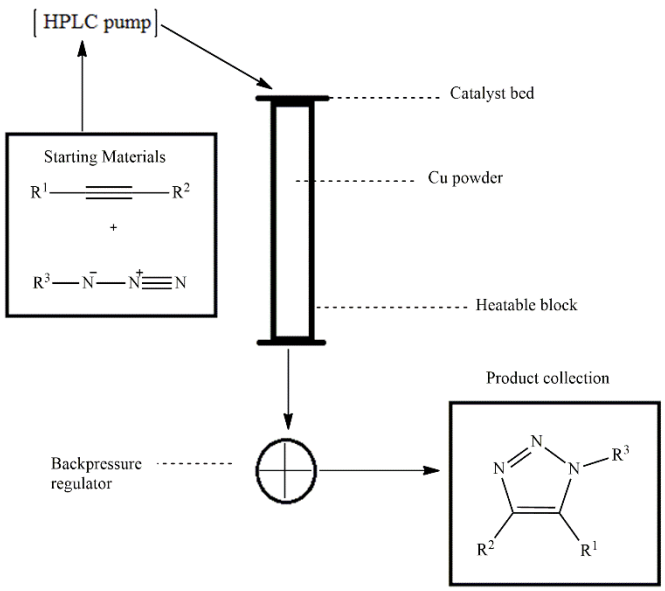


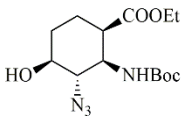
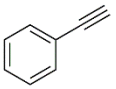
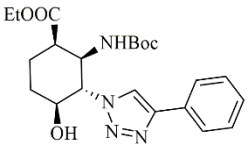
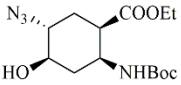
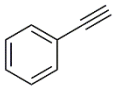
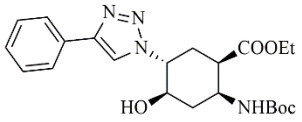
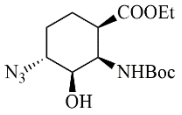
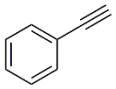
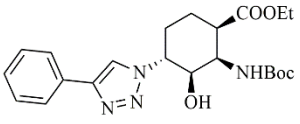
Figure 25. Continious flow experimental setup

When exposed to air, copper constantly oxidizes and non-self-protecting layers like Cu_2O are formed on the surface. Copper powder was placed in stainless steel column as a catalyst bed. The column was then put to the Peltier heating device that can heat column up to 100 °C and 100 bar were achieved by backpressure regulator. Reactants were continuously pumped into the column by HPLC pump.

Recent publication showed that addition of particular acid can further accelerate the reaction and avoid the accumulation of unwanted byproducts. On the other hand, formation of byproduct is catalyzed by base. In literature, the base diisopropylethyl-amine (DIEA) and HOAc as an acid are the mostly referred. Both were used during reactions, each in 0.04 eq, at room temperature and at 100 bars.

Each reaction mixture was pumped by HPLC pump in aliquots of 2.5 cm^3 (1eq of azide;1.5eq of alkyne) with a flow rate of 0.5 ml/min. Consecutively, it was possible to reduce temperature to the rt and in presence of additives to setup reaction conditions B (Table 3.) to the more stable. By using conditions A, regioselectively 1,4-disubstituted 1,2,3-triazole isomers were obtained. High pressure and temperature conditions led to good yields but when temperature was reduce to rt, finall product yield was excelent for each reaction (Table 3). [19]

Table 3. 1,2,3-triazole-subtituted alicyclic β-amino acid derivates synthesized by contious flow

	Azide (1 eq)	Acetylene (1.5 eq)	Product	Yield (%) A	Yield (%) B
1.				61	96
2.				47	97
3.				33	76

Conditions: **A** - CH_2Cl_2 as a solvent, 100 bar, 100°C, flow 0.5 ml/min, no additives
B - CH_2Cl_2 as a solvent, 100 bar, r.t., flow 0.5 ml/min, 0.04 eq of DIEA + 0.04 eq of HOAc

2.2 Click synthesis of 1,4-disubstituted-1,2,3-triazole catalysed by CuO-CeO_2 nanocomposite in the presence of amberlite-supported azide

Nanocrystalline metal oxides were applied in laboratory as well as in the industry in the past. Moreover, positive side of nanocrystalline oxides is good activation of absorbed compounds, selectivity, reaction rate enhancement, and easy work-up. In organic chemistry, nanocomposite metal oxides have been more frequently used as catalyst due to their large surface.

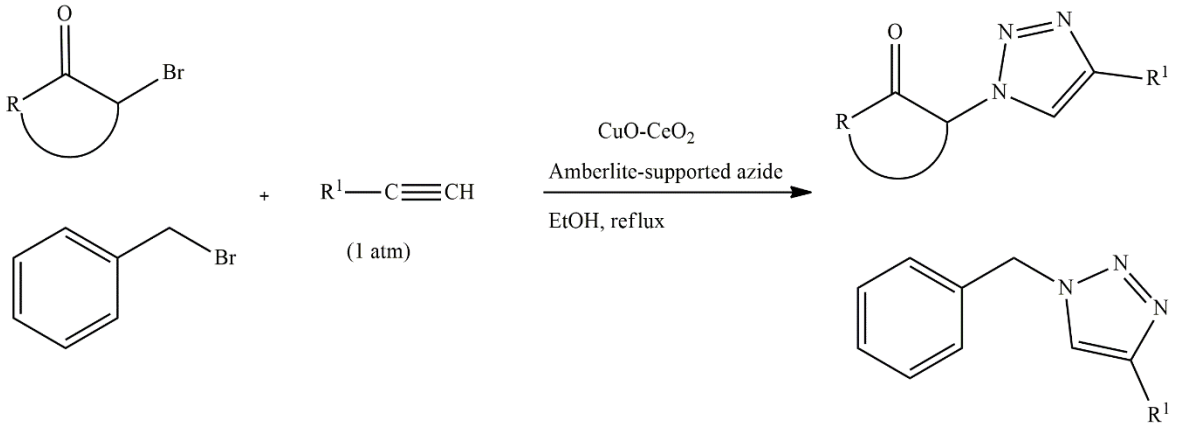


Figure 26. Nanocomposite-catalysed click synthesis of 1,4-substituted 1,2,3-triazole in presence of CuO-CeO_2

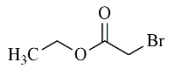
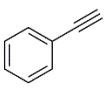
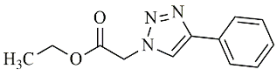
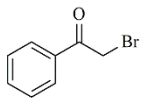
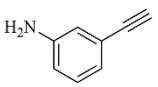
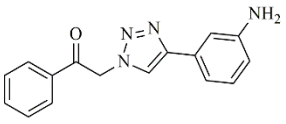
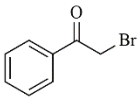
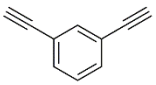
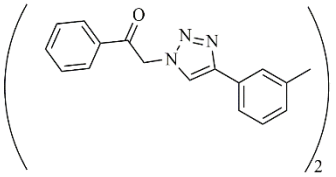
Sodium azide is typical reactant for azide-alkyl cycloaddition. However, use of excess sodium azide for nucleophilic substitution can lead to pollute the environment because is not often possible to recover it from reaction mixture. This problem was solved by Khatam et al. who reported multicomponent synthesis of triazole derivatives by amberlite-supportet azide as the source of azide ion. Azide ion was generated by ion exchange using aqueous 10 % NaN_3 solution.

In this research, amberlite supported azide was used in presence of CuO-CeO_2 nanocomposite to synthesize differently substituted 1,4-disubstituted-1,2,3-triazoles in good yield. Reuse of catalyst without any significant reduce of catalytic activity is one of the most important advantage of this method. Nanocomposite CuO-CeO_2 have been prepared in aqueous solution of copper nitrates, cerium and KOH under vigorous stirring at constant tem-

perature and pH. In next step, the solution was filtered, washed and calcined for final purification of catalyst.

The highest yield was achieved using benzyl bromide and phenyl acetylene in EtOH as a solvent. Other solvents, like MeOH, CH_2Cl_2, CH_3CN, and water gave slightly lower yields.[20]

Table 5. Cu-CeO_2 nanocomposite-catalyzed click synthesis of triazole derivates

	Substrate	Alkyne	Product	Time (min)	Yield (%)
1.				90	88
2.				90	89
3.				120	89

2.3 1-Monosubtituted 1,2,3-triazole synthesis via click chemistry in water

Recent publications has showed that 1-monosubstituted 1,2,3-triazoles have important biological activity. Preparation of such compounds requires high temperature conditions and organic solvent. However, green medium such as water has attracted attention in chemical society in last decades. Team of researchers from Hainan Normal University used organic azides and acetylene gas in presence of CuI in water to synthesize 1-monosubstituted 1,2,3-triazoles.

Contrary to previous studies, which showed that presence of water in organic solvents has negative influence on click chemistry of organic azides with calcium carbide or acetylene

gas, Luyong Wu. et. al. surprisingly found a way to overcome this disadvantage and showed that reaction can be carried out even in water medium.

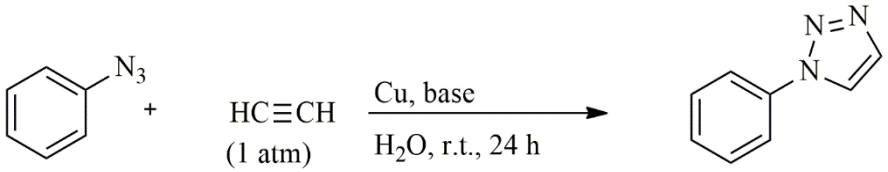
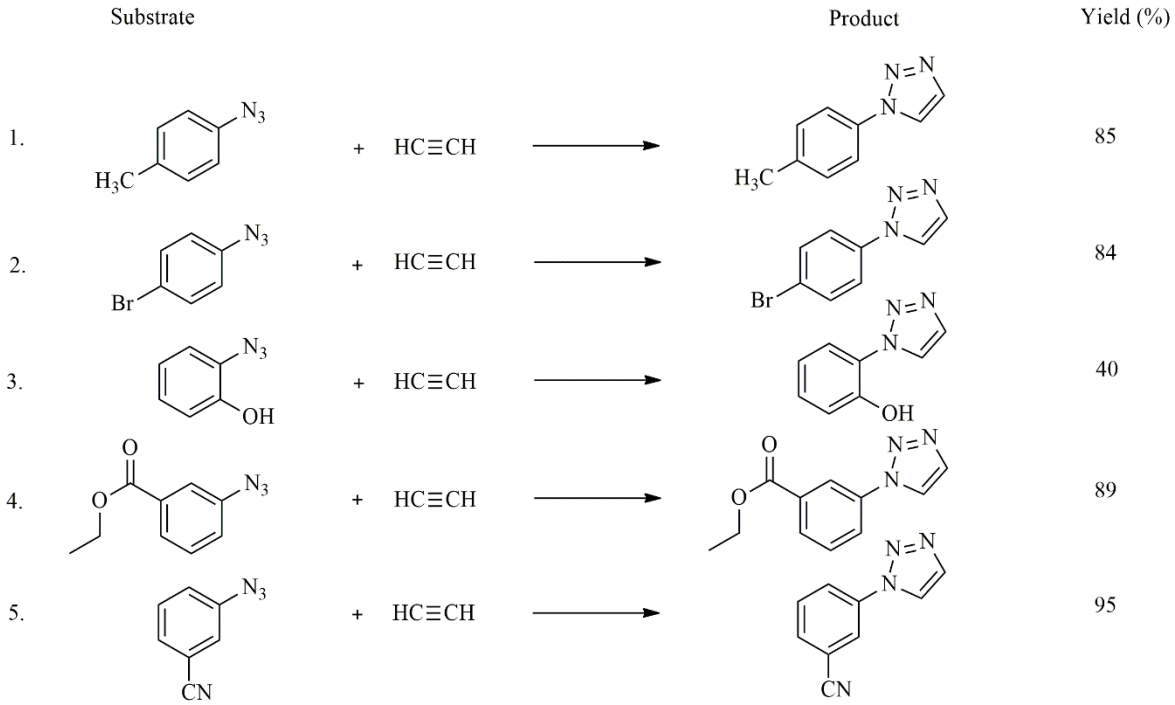


Figure 27. Initial reaction conditions for click synthesis of 1-monosubstitued 1,2,3-triazole in water

Final results showed that electron-reach and electron-poor aromatic azides were proceed giving high yield products, apart those with substituents in ortho positions. This research also showed that effectiveness of this green synthesis in comparable with other click reaction in organic solvent.[21]

Table 6.Synthesis of differently substituted triazoles under optimal conditions



II. ANALYSIS

3 EXPERIMENTAL PART

3.1 General Methods

Melting points were measured using a Kofler block and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz for ^{1}H and 75.77 MHz for ^{13}C. ^{1}H and ^{13}C NMR chemical shifts were referenced to the solvent signals (^{1}H: δ(residual $CHCl_3$)=7.27 ppm, δ(residual [D_5]DMSO)=2.50 ppm, δ(residual CD_2HOD)=3.31 ppm; ^{13}C: δ($CDCl_3$)=77.23 ppm, δ([D6]DMSO)=39.52 ppm, δ([D_4]methanol)=49.15 ppm). The IR spectra were recorded using KBr discs with a Mattson 3000 FT-IR instrument and was reported in cm^{-1}. The GC-MS analyses were conducted on a Shimadzu QP-2010 instrument using a Supelco SLB-5ms (30 m, 0.25 mm, 0.25 μm) column. Helium was used as the carrier gas in the constant linear flow mode (38 $cm \cdot s^{-1}$); the column was held at 100 °C for 7 min and then increased at the rate of 25 °C/min to 250 °C before holding for the required time. Only peaks with relative abundances exceeding 5% were listed.

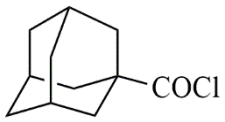
3.2 Chemicals

Thionyl chloride ($SOCl_2$), toluene (dried over sodium metal), xylene (dried over sodium metal), diethyl ether (dried over sodium metal), potassium carbonate (K_2CO_3), ammonium chloride (NH_4Cl), benzoyl peroxide (BPO), *N*-bromosuccinimide (NBS), carbon tetrachloride (dried by distillation from phosphorus pentoxide), sodium bicarbonate ($NaHCO_3$), sodium iodide (NaI), dimethyl sulfoxide (dried by vacuum distillation and subsequent treatment with molecular sieves 4A), sodium hydroxide (NaOH), periodic acid (H_5IO_6), chromium(III) acetylacetonate ($Cr(AcAc)_3$), acetonitrile (CH_3CN), bromine(Br_2), chloroform ($CHCl_3$), petroleum ether 40–60 °C fraction (PE), potassium *tert*-butoxide, *tert*-butyl alcohol, acetone, sodium azide (NaN_3), copper(I) iodide (CuI), sulfuric acid (H_2SO_4), sodium nitrite ($NaNO_2$), rhodium(II) acetate dimer $Rh_2(OAc)_4$, Tetrakis(acetonitrile)copper(I) hexafluorophosphate ($Cu(I)(CH_3CN)_4PF_6$), copper (Cu), ethanol (EtOH), and silica gel 60 were purchased from Sigma Aldrich. (4-((Adamantane-1-carbonyl)phenyl)triphenylphosphonium was prepared for some other purpose and was used courtesy of other students.

3.3 Synthesis of adamantane-1-carbonylchloride

Adamantane-1-carboxylic acid (32 g, 83.32 mmol) was dissolved in 30 cm^3 of dried toluene. Small portion of $SOCl_2$ was added under continuous stirring and mixture was heated up to 65 °C. During next 90 minutes, an additional portion of $SOCl_2$ (12.88 g, 108.3 mmol) dissolved in toluene (10 cm^3), was added to reaction mixture. The mixture was stirred for 8 hours and a portion of dry toluene (20 cm^3) was added. Subsequently, the same amount of toluene that was distilled off (20 cm^3). This operation was repeated three times. Finally, the solvent volume was reduced and the mixture was allowed to crystallize overnight at −18 °C. Next day, thin, slightly yellow crystals were collected via filtration under an inert atmosphere. After filtration, pale yellow crystals were dried in argon stream.

Name:	adamantane-1-carbonyl chloride (**II**)
Formula:	$C_{11}H_{15}ClO$
M_r	198.69



Yield: 12.88 g, 75 %

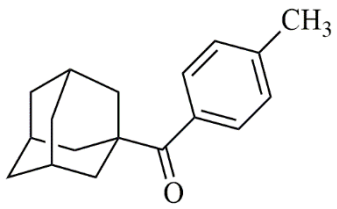
Melting point: 46–51 °C

3.4 Synthesis of adamantan-1-yl(4-methylphenyl)methanone

Previously dried three-necked flask was equipped with rubber septum, thermometer and stirrer. Initially, CuCl (0.17g, 1.18 mmol) and LiCl (0.15 g, 3.63 mmol) were dissolved in THF. Subsequently, $AlCl_3$ (0.24 g, 1.18 mmol) was added to solution and dissolved. Adamantane-1-carbonylchloride **I** (5 g, 25.16 mmol) was added in the next step and solution was stirred for 5 minutes. Additionally, *p*-tolylmagnesium bromide was prepared by refluxing 4-methyl-1-bromotoluene (5 cm^3, 37.47 mmol) with an excess of magnesium turnings (1.37 g, 56.6 mmol) in 10 cm^3 of dry DEE. *P*-tolylmagnesium bromide was added through the septum, within next 30 min. The reaction mixture was refluxed for 1 h. Subsequently, heating was turned off and reaction mixture sediment over night. Next day unreacted Grignard reagent was neutralized with 15 cm^3 of HCl (1 M solution). After 15 minutes, the reaction mixture was extracted with 3 × 30 cm^3 DEE, 2 × 20 cm^3 K_2CO_3 (1 M solution) , and 1 × 15 cm^3 NH_4Cl (3 M solution). Collected organic portions were dried

over Na_2SO_4 and solvent was evaporated on a rotary evaporator to obtain a white powder. Pure product was subsequently crystallized from hexane.

Name:	Adamantan-1-yl(4-methylphenyl)methanone(**V**)
Formula:	$C_{18}H_{22}O$
M_r	254.37



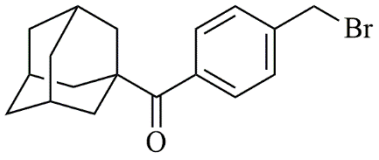
Yield: 14 g, 85 % of crystallized product

MS (EI 70 eV):65 (6), 67 (6), 79 (14), 91 (15), 93 (15), 107 (9), 119 (17), 135 (100), 254 (12) m/z (%).

3.5 Synthesis of adamantan-1-yl(4-(bromomethyl)phenyl)methanone

Adamantan-1-yl(4-methylphenyl)methanone 5 g (19.66 mmol) was dissolved in dried carbon tetrachloride. In next step, *N*-bromosuccinimide (3.55g, 19.66 mmol) was added, while the reaction was activated with tungsten 60 W lamp and a small amount of benzoyl peroxide. The reaction mixture was heated up to 80 °C (reflux) and monitored by thin layer chromatography (TLC). After the whole amount of starting compound reacted, *N*-bromosuccinimide was separated by filtration and solvent was removed using rotary evaporator. Obtained crude product was crystallized to give pure adamantan-1-yl(4-(bromomethyl)phenyl)methanone.

Name:	Adamantan-1-yl(4-(bromomethyl)phenyl)methanone(**VI**)
Formula:	$C_{18}H_{21}BrO$
M_r	333.26



Yield: 4.1 g, 63 %

IR: 3422 (w), 2952 (w), 2904 (w), 2847 (w), 2363(w), 2344 (w), 2103 (s), 1723(s), 1655(w), 1613 (w), 1436 (m), 1414 (w), 1344 (w), 1252 (s), 1193(m), 1178 (m), 1109 (s), 1002 (w), 846 (w), 756 (m), 712(w), 669 (w), 558 (w) cm^{-1}.

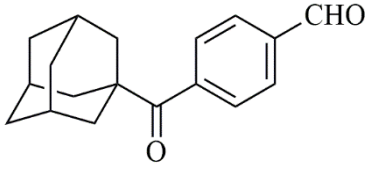
MS (EI 70 eV): 79 (13), 90 (5), 93 (12), 107 (7), 118 (22), 135 (100), 136 (10), 253 (7) m/z (%).

3.6 Synthesis of 4-(1-adamantylcarbonyl)benzaldehyde

Adamantan-1-yl(4-(bromomethyl)phenyl)methanone (8,04 g,24 mmol) was dissolved in previously dried DMSO. Before reaction started, whole apparatus was heated under vacuum to remove traces of water. Additionally, sodium iodide (2.03g, 24 mmol) and sodium bicarbonate (3.59 g, 24 mmol) were added. The reaction mixture was heated at 120 °C for 6 h. The reaction was monitored by GC-MS.

The cooled reaction mixture was poured onto crushed ice. After the ice melted, the crude product changed its physical properties from liquid to solid. The organic portion was dissolved with DEE and washed with brine. After drying over Na_2SO_4, crude product was washed with *n*-hexane and filtered. Product (aldehyde) was separated from its reduced form (alcohol) by column chromatography (SiO_2, PE:EA=4:1, v:v) with silica gel as a stationary phase.

Name:	4-(1-adamantylcarbonyl)benzaldehyde (**VII**)
Formula:	$C_{18}H_{20}O_2$
M_r	268.35



Yield: 5.6 g, 88 %

MS (EI 70 eV): 67 (7), 77 (9), 79 (15), 93 (16), 107 (10), 135 (100), 136 (11), 268 (8) m/z (%).

3.7 Synthesis of 4-(1-adamantylcarbonyl)benzaldehydefrom adamantan-1-yl(4-(hydroxymethyl)phenyl)methanone

Periodic acid (0.62 g, 27.6 mmol) and chromium(III) acetylacetonate (0.064g, 10% mol) were dissolved in 12 cm^3 of acetonitrile. Then, adamantan-1-yl-(4-

(hydroxymethyl)phenyl)methanone (0.5g, 18.4 mmol) was added. The reaction was continued under argon at room temperature for next 5 h. Initially, the reaction mixture was diluted with 55 cm^3 of EA and then washed with distilled water. Inorganic part appeared as precipitant. In next step saturated solution of sodium sulfate and brine were used to finalize purification. Obtained organic solution was dried over Na_2SO_4. Product (aldehyde) was separated from its reduced form (alcohol) by column chromatography (SiO_2, PE:EA=4:1, v:v), with silica gel as a stationary phase.

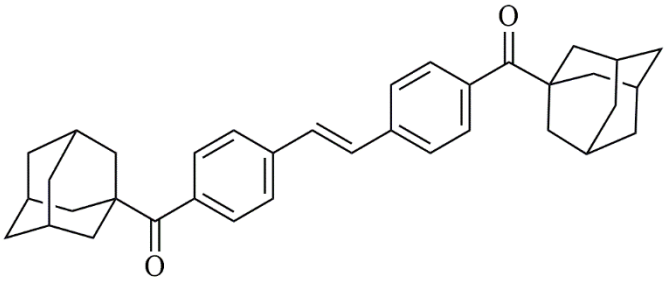
Yield: 0.42 g, 87.9 %

MS (EI 70 eV): 67 (7), 77 (9), 79 (15), 93 (16), 107 (10), 135 (100), 136 (11), 268 (7) m/z (%).

3.8 Synthesisof 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethene

4-(1-Adamantylcarbonyl)benzaldehyde (1.72 g, 6.64 mmol) and 4-(adamantane-1-carbonyl)phenyl)triphenylphosphonium-bromide (3.83 g, 6.44 mmol) were dissolved in 123 cm^3 of CH_2Cl_2 in the round bottom flask. In next step, 82 cm^3 (0.1 M) of NaOH was added. Heterogeneous solution was stirred at room temperature for 6 h. Reaction progress was monitored by TLC. Once reaction finished, the mixture was diluted with 15 cm^3 of $CHCl_3$. After this, the water phase was washed with 3×15 cm^3 of $CHCl_3$. The organic phase was dried over Na_2SO_4 and solvent was removed on rotary evaporator. Obtained product was dissolved in $CHCl_3$ and poured trough a celite pad to remove highly polar unreacted 4-(adamantane-1-carbonyl)phenyl)triphenylphosphonium-bromide and Ph_3PO. Nevertheless, the purity of the product was not satisfactory. Therefore, the fine product was achieved by column chromatography in pure chloroform with silica gel as a stationary phase.

Name:	1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethene (**X**)
Formula:	$C_{36}H_{40}O_2$
M_r	504.7



Yield: 258 mg, 80 %

Melting point: 135–139 °C

IR: 3050 (w), 2847 (s), 1659 (s), 1600 (m), 1552 (w), 1438 (s), 1350 (w), 1269 (m), 1231 (m), 1189 (s), 1120 (s), 1072 (w), 989 (m), 947 (w), 927 (w), 886 (w), 808 (w), 721 (s), 697 (s), 543 (s), 499 (w), 456 (w) cm^{-1}.

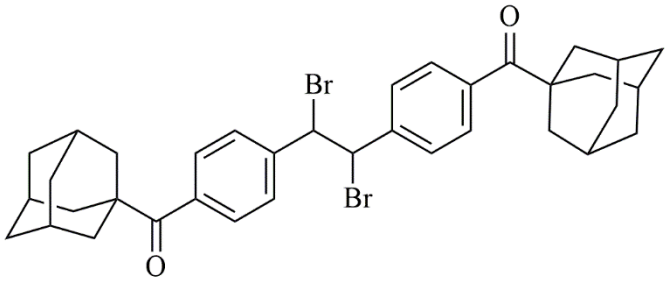
^{1}H NMR ($CDCl_3$)**:** δ 7.50–7.48 (d, *J*=10 Hz, 4H), 7.27–7.25 (d, *J*=10 Hz , 4H), 6.66 (s, 2H), 2.08-2.02 (m, 13H), 1.77–1.75 (m, 14) ppm.

^{13}C NMR ($CDCl_3$): 209.2, 139.03, 138.1, 130.6, 127.6, 77.01, 46.9, 39.2, 36.5, 28.1 ppm.

3.9 Synthesis of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)-1,2-dibromoethane

1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethene (0.28g, 0.55 mmol) was dissolved in 5 cm^3 of $CHCl_3$ in 50 cm^3 round bottom flask. Then, bromine (0.58 mmol) was dissolved in another 5 cm^3 of $CHCl_3$ and added dropwise via syringe to the round bottom flask. The reaction was stirred for next 3 h under argon and at room temperature. In next step, the reaction mixture was diluted with $CHCl_3$ and washed 2 × 15 cm^3 $Na_2S_2O_3$, 3 × 15 cm^3 H_2O, and 1 × 15cm^3 Brine. The organic phase was dried over Na_2SO_4 and solvent was removed by rotary evaporator. The crude product was obtained as a white fluffy powder.

Name:	1,2-bis(4-(1-adamantylcarbonyl)phenyl)-1,2-dibromoethane (**XI**)
Formula:	$C_{36}H_{40}Br_2O_2$
M$_r$	664.51



Melting point: 263–271 °C

Yield: 339 mg, 92 %

IR: 3114 (w), 2849 (s),2677 (w),2657 (w),2359 (w), 1888 (s),1771 (w),1771 (w),1667 (s),1604 (w),1451 (w),1409 (w),1344 (w),1270 (s),1235 (s),1176 (w),1152 (w),1114 (w),1103 (w), 1015 (w), 988 (m),930 (m),845(m),797(w),751 (m),702 (m),667 (m),622 (w),603 (w),545 (w),464(w) cm^{-1}.

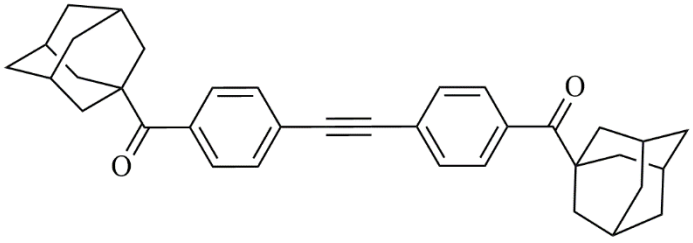
^{1}H NMR ($CDCl_3$)**:** δ 7.54–7.53 (d, *J*=8.4 Hz, 2H), 7.45–7.43 (d, *J*=8.4 Hz, 2H), 7.31–7.29 (d, *J*=8.4 Hz, 2H), 7.13–7.11 (d, *J*=8.4 Hz, 2H), 5.38–5.36 (d, *J*=6.9 Hz, 2H), 2.02–1.95 (m, 13H), 1.86–1.85 (m, 5H), 1.72–1.61(m, 12H) ppm.

^{13}C NMR {^{1}H} ($CDCl_3$): δ 209.2, 139.3, 130.6, 128.4, 127.6, 126.1, 46.9, 39.2, 36.6, 28.1 ppm.

3.10 Synthesis of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne

1,2-bis(4-(1-adamantylcarbonyl)phenyl)-1,2-dibromoethane (1 g, 1.15 mmol) was dissolved in *tert*-butyl alcohol. The reaction mixture was heated up to 110 °C. Then, potassium *tert*-butoxide (1.38g,12.29 mmol) was added. The reaction progress was monitored by TLC (SiO_2, PE:EA=16:1, v:v). After 3 h, the reaction was worked up. The reaction mixture was poured onto crushed ice and then washed with CH_2Cl_2 (6 × 20 cm^3). Collected organic portions were washed with water (3 × 20 cm^3) and dried over Na_2SO_4.The crude product was finally purified using column chromatography (SiO_2, $CHCl_3$:PE=1:1, v:v).

Name:	1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne (**XII**)
Formula:	$C_{36}H_{40}O_2$
M_r	502.69



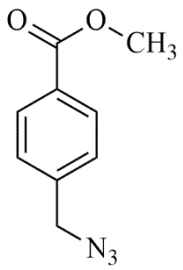
Yield: 567 mg, 75 %

IR: 2941 (m),2903 (s),2849 (m), 2680 (w),2657 (w),2363 (w),2345 (w),1657 (s), 1602 (w),1552(w),1449 (w),1403 (w),1344 (w), 1269 (m),1233 (m), 1172 (m), 1112 (w),1045 (w),990 (m), 952 (w),929 (w), 846 (m),752 (w),681 (w),611 (w),511 (w), 460 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$)**:** δ 7.45–7.43 (d, *J*=8.2 Hz, 4H), 7.11–7.09 (d, *J*=8.1 Hz, 4H), 1.99–1.94 (m, 13H), 1.68–1.66 (m, 12H), 1.26–1.21 (m, 5H) ppm.

3.11 Synthesis ofmethyl 4-(azidomethyl)benzoate

Methyl 4-bromobenzoate (100 mg, 0.43 mmol) was dissolved in 10 cm^3 of acetone in 50 cm^3 round bottom flask. Subsequently, sodium azide (42.57mg, 0.65mmol) was added. The reaction was heated up to 60 °C and monitored by TLC. After 2 h, the reaction mixture was cooled down and then poured onto ice. The water phase was washed with 3 × 10 cm^3 of chloroform and then dried over Na_2SO_4. Chloroform was removed using rotary evaporator and final purification was achieved by column chromatography (SiO_2, $CHCl_3$:PE=1:1, v:v).

Name:	methyl 4-(azidomethyl)benzoate (**XIV**)	
Formula:	$C_9H_9N_3O_2$	
M_r	191.19	

Yield: 78 mg, 94 %

^{1}H NMR ($CDCl_3$)**:** δ 8.07–8.05 (2H, dd, *J*=9, 2 Hz), 7.41–7.39(2H, dd, *J*=8, 2 Hz), 4.42 (s, 2H), 3.93 (s, 3H) ppm.

3.12 Synthesis of ethyl diazoacetate

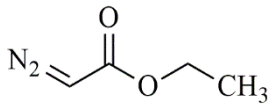
Initially, ethyl glycinate hydrochloride (4 g, 28.65 mmol) was dissolved in 7.14 cm^3 of water and then was mixed with dichloromethane (17.14 cm^3). A double-wall reactor, which was equipped with stirrer, thermometer, dropping funnel, was employed to allow precise temperature maintenance using an external chiller. Sodium nitrite (2.37g, 34.3 mmol) was added to the prepared solution and temperature was lowered to −9°C. Then, sulfuric acid (2.71 g, 5% (by weight)) was added dropwise via syringe. During the sulfuric acid addition, it was important not to exceed 1°C because of highly exothermic reaction. The reaction was terminated after half an hour, once the heat was no longer evolved. The

reaction mixture was poured onto crushed ice. The yellow dichloromethane phase was separated and washed with 5 % sodium bicarbonate solution. Then, the aqueous layer was extracted with 1 × 30 cm^3 of dichloromethane. Both phases, dichloromethane and sodium bicarbonate were shaken till traces of sulfuric acid remains. This was monitored by pH paper as an indicator. In next step, the yellow organic phase was separated and dried over Na_2SO_4. Later, the solvent was removed by rotary evaporator to get yellow oil (ethyl diazoacetate).

Yield: 2.77 g, 85%

MS (EI 70 eV): 41 (57), 42 (31), 69 (100), 86 (5), 43 (19), 44 (9), 45 (14), 114 (81), 57 (9.83), 58 (12) m/z (%).

Name:	Ethyl diazoacetate
Formula:	$C_4H_6N_2O_2$
M_r	114.1



3.13 Reaction of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne with methyl 4-(azidomethyl)benzoate

1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne (0.1g, 0.19 mmol) was dissolved with freshly dried 5cm^3 DMSO in 50 cm^3 round bottom flask. Than methyl 4-(azidomethyl)benzoate (37.82 mg, 0.19 mmol) and copper(I) iodide (19 mg, 0.1 mmol) were added. Reaction mixture was heated up to 110 °C under stirring and kept under $CaCl_2$ for next 35 h. Temperature was then increased up to 150 °C for next 10 h in aim to initiate reaction. Reaction progress was monitored by TLC and no changes in reaction mixture composition were observed.

3.14 Reaction ofethyne-1,2-diylbis(4,1-phenylene))bis((adamantan-1-yl)methanone with sodium azide

This reaction was performed twice under the same reaction conditions, but with different reaction scale. In first case, sodium azide (97.28 mg, 0.4 mmol), copper(I) iodide(19.04 mg, 0.1 mmol), and in second case sodium azide(19.26 mg, 0.08 mmol), copper(I) iodide

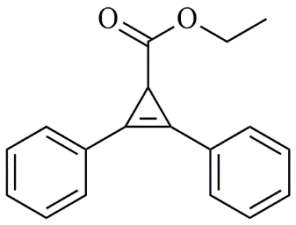
(3.76 mg, 0.02 mmol) were used. Initially,1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne (100 mg, 0.2 mmol) was dissolved in 5cm^3 of dried DMSO and then sodium azide and copper(I)iodine was added. The reaction was heated up to 110 °C for 21 h and no changes were observed. Then the temperature was increased up to 150 °C for next 14 h. Reaction progress was monitored by TLC and no changes in reaction mixture composition were observed.

3.15 Reactions of diphenylethyne and ethyl diazoacetate

Rhodium(II)acetate (6 mg, 13.6 μmol) was dissolved with 4 cm^3 of dichloromethane in 50 cm^3 round bottom flask. Subsequently, diphenylethyne (200 mg, 1.12 mmol) was added. Diazoacetate (0.63 g, 5.6 mmol) was dissolved in 2 cm^3 of dichloromethane and added to the reaction mixture by a syringe pump (3.7 μl/min). The mixture was stirred under argon at room temperature for 9 h. Reaction progress was monitored by GC-MS.

This reaction was repeated with tetrakis(acetonitrile)copper(I) hexafluorophosphate(4.17 mg, 11.2 μmol) instead of rhodium(II)acetate as a catalyst. Additionally, elemental copper (13.5 mg, 0.212 mmol) at room temperature and 40 °C was also tested, respectively.

Name:	Ethyl 2,3-diphenylcycloprop-2-enecarboxylate
Formula:	$C_{18}H_{16}O_2$
M_r	264.32



Yield: 240 mg, 81%

MS (EI 70 eV): 50 (27), 51 (28), 52 (5), 63 (5), 74 (9), 75 (25), 76 (26), 77 (46), 78 (8), 89 (5), 89 (6), 91 (7), 102 (52), 103 (13), 104 (32), 105 (15), 119 (14), 121 (9), 130 (100), 131 (10), 132 (89), 133 (18), 149 (27), 150 (5), 160 (11), 161 (23), 162 (14), 163 (30), 164 (8) m/z (%).

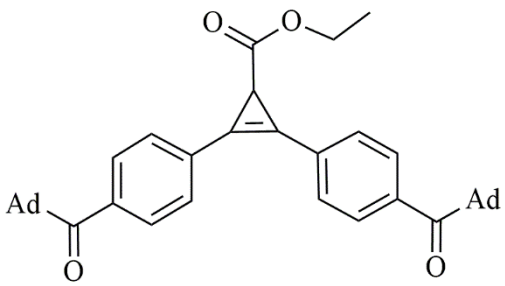
3.16 Reaction of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne and diazoacetate catalysed with tetrakis(acetonitrile)copper(I) hexafluorophosphate

The reaction was performed under an argon atmosphere at room temperature for 10 h. Procedure was essentially the same as that described previously for the model reaction. Progress of the reaction was monitored by TLC. After 10 h, the reaction mixture was poured onto crushed ice. Once ice completely melted, the water phase was washed with 3 × 15 cm^3 dichloromethane. Collected organic portions were washed with brine. Traces of water were taken away with Na_2SO_4 and then the solvent was removed with a rotary evaporator. Final purification was performed using column chromatography (SiO_2, $CHCl_3$:PE=4:1,v:v).

3.17 Reaction of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne and diazoacetate catalysed with copper

The whole apparatus was dried with heat gun and xylene was freshly distilled from sodium metal. Initially,1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne (0.1 g, 0.2 mmol) of was dissolved in 2 cm^3 of dry xylene. Subsequently, copper (12 mg, 0.19 mmol) was added and the reaction was heated up to 140°C. Solution of diazoacetate (0.13g, 0.19 mmol) in xylene (2 cm^3) was added using syringe pump within 10 h. Reaction progress was monitored by TLC and two new spots were observed. Reaction work up and purification has been done in the same way as it was described in the previous reaction.

Name:	ethyl 2,3-bis(4-(adamantane-1-carbonyl)phenyl)cyclopropanecarboxylate
Formula:	$C_{40}H_{46}O_4$
M_r	590.79



4 DISCUSSION

4.1 Preparation of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne

My previous bacherol research was focused on the proposal of a model reaction for the future synthesis of ditopic ligands based on adamantine and 1,2,3-triazole. Two main compounds, (6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl) hexanoic acid and 4-((4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoate) were successfully synthesized. This aim was achieved through 1,3-dipolar cycloaddition, radical reaction, esterification and nucleophilic substitution.

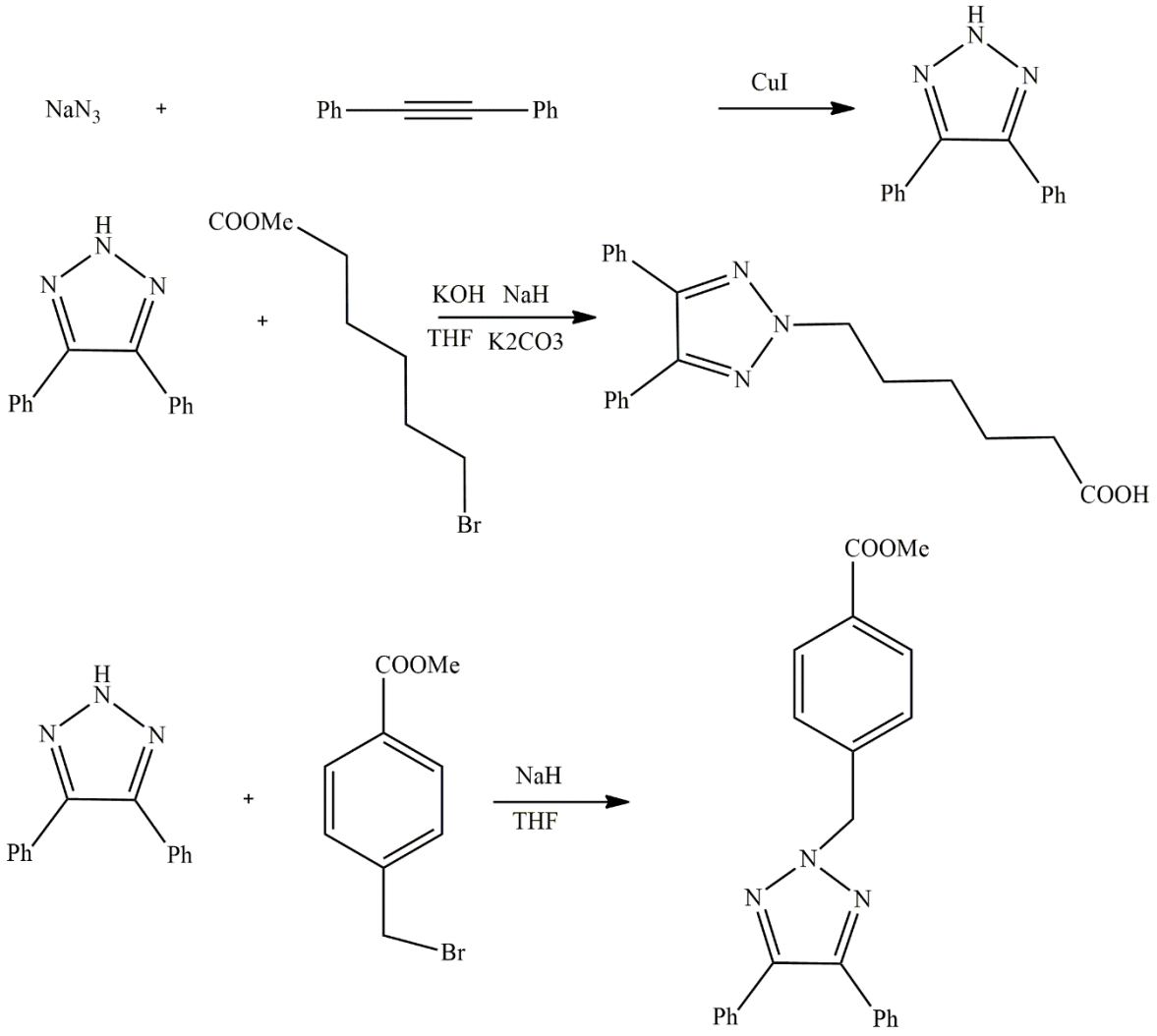


Figure 28. Proposal of a model reaction for the synthesis of ditopic ligands based on adamantine and 1,2,3-triazole

As a logical extension, the purpose of master's thesis was to apply synthetic strategies based on 1,3-dipolar cycloaddition to final preparation of ditopic ligands based on adamantane and 1,2,3-triazole. This required preparation of key intermediate – compound **XII**. It was prepared using following reaction strategy: a sequence of nucleophilic substitution, Grignard reaction, radical bromination, Wittig reaction, electrophilic addition, and elimination in final step. This synthetic approach is depicted in Figure 28.

How it was already mentioned above, this work continuous research of bachelor thesis. Described model reactions were applied, after starting compound **XII** was prepared. In the first step, compound **XII** should be transformed through copper catalyzed azide-alkyl cycloaddition (CuAAC) to give 1,2,3-triazole based on adamantane. Triazole should be latter differently substituted in positions N-1 and N-2 through nucleophilic substitution.

Adamantane-1-carbonyl chloride (**II**) was prepared from adamantane-1-carboxylic acid (**I**) in presence of thionyl chloride in toluene .Toluene (20 cm^3) was added and distillated again after 8 hours. Unreacted thionyl chloride was in this way removed as a azeotropic mixture with toluene.

In the next step, adamantane-1-carbonyl chloride reacted with previously prepared Grignard reagent *p*-tolylmagnesium bromide (**IV**) to give adamantan-1-yl((4-methylphenyl)methanone) (**V**). Reaction was performed in DEE under catalysis by $AlCl_3$, LiCl, and CuCl. Crystallization was repeated three times with aim to improve final yield. In first fraction was obtained clear product. Next two crystallizations provided a product, which further purification by column chromatography was needed. Compound **V** was then transformed to adamantan-1-yl(4-(bromomethyl)phenyl)methanone (**VI**) via radical reaction with NBS in carbon tetrachloride. Adamantane-1-carbonyl)benzaldehyde (**VII**) was prepared from compound **VI** in DMSO. This transformation was achived by NaI and $NaHCO_3$. As some side products appeared in the crude mixture after conversion of compound **VI** to aldehyde, (Figure 29), the mixture had to be separated using column chromatography. The crude product was not completely soluble in *n*-hexane or in mixture PE:EA=4:1.Thus, crude solid was dissolved in EA, loaded into the column, and then eluted with PE:EA=4:1as a mobile phase.

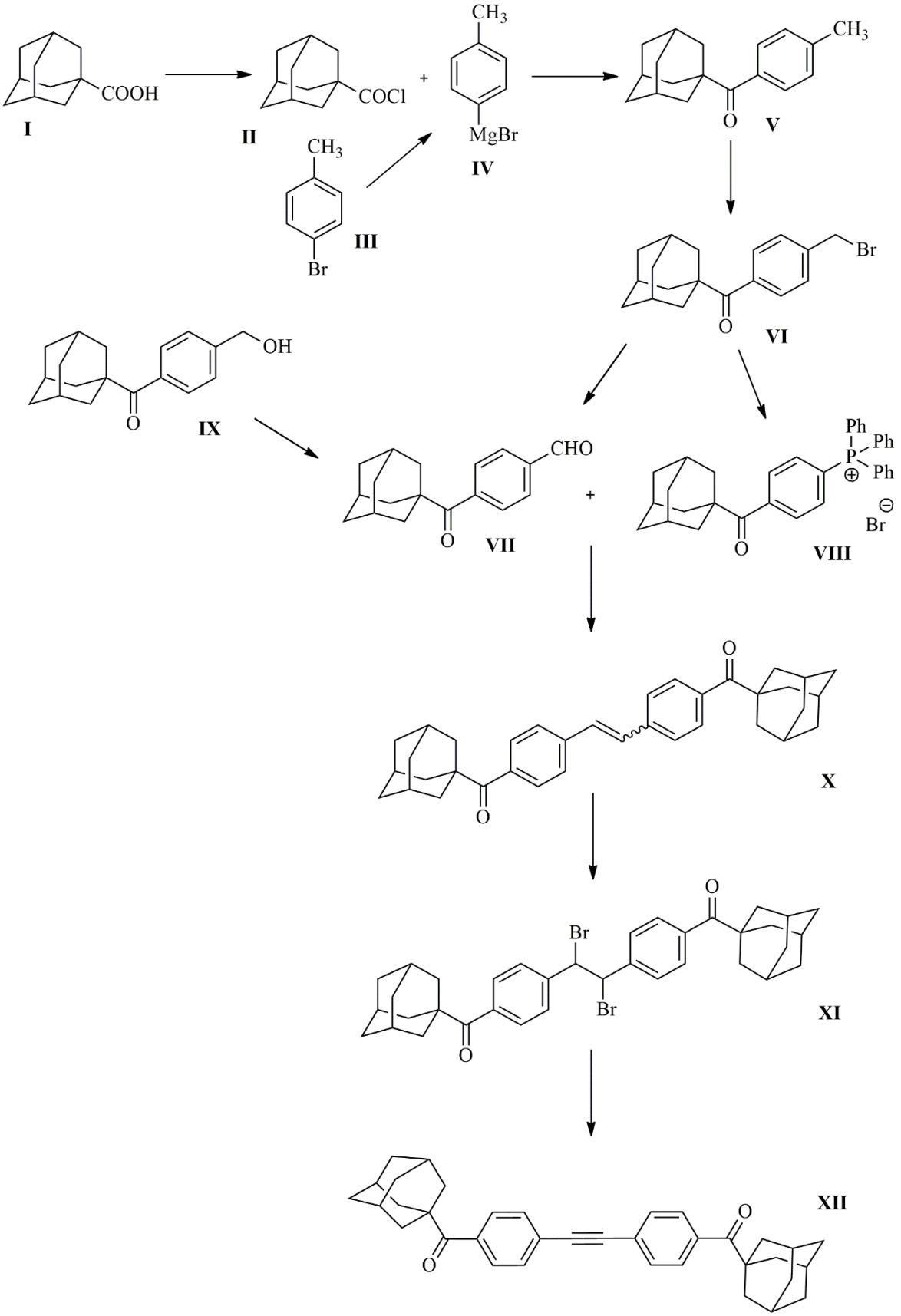


Figure 29. Preparation of 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne

During work up procedure and purification, compound **VII** was steadily oxidized to compound **IX**. Therefore, because of the huge loss of compound **VII** that supposed to be used in next reaction, it was necessary to find an alternate convenient method for reduction of compound **IX** to **VII**. This was achieved in CH_3CN as a reaction medium using H_5IO_6 and 10 % mol $Cr(AcAc)_3$ as a catalist at room temperature. In the final step, the separation was performed by column chromatography (SiO_2, PE:EA=4:1, v:v) with the satisfactory conversion of 88 %. Before compound **XII** was prepared in this step was recorded highest loss. This was caused by the low stability of compound **VII**. To avoid oxidation of compound **VII**, it was always stored under −18 °C and under argon atmosphere.

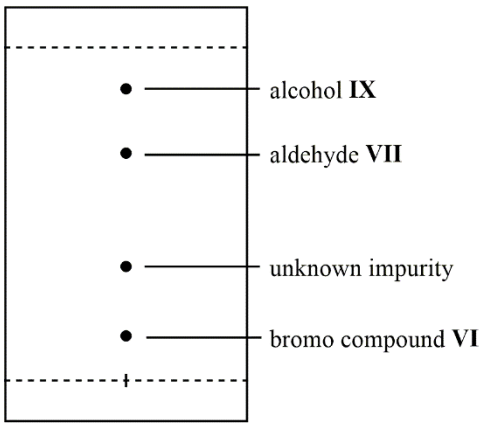


Figure 30. Schematic representation of products on TLC, after synthesis of compound **VII**

Compound **VII** was prepared by another group of students and was used in the reaction with compound **VIII** to give 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethene. While the reaction was going on, color of the reaction mixture changed from slightly orange to final yellow color. In organic phase (CH_2Cl_2), a solid material appeared. Triphenylphosphine oxide was observable as a byproduct of this reaction on the base line of TLC. The final product appeared at R_f=0.81.Unfortunately, despite the significant difference in the R_f values of those two compounds, it was quite difficult to find an optimal solvent for their separation. Triphenylphosphine oxide was partially soluble in chloroform. Thus, compound **X** was always eluted from column together with Ph_3PO and separation was not possible. Therefore, considerable efforts have been made with the use of celite and pure chloroform. Once purification with celite has been done, solvent from the filtrate was removed by rotary evaporator and product was separated by column chromatography with pure chloroform

as mobile phase. Final compound **X** was obtained as a white powder in two diastereomer forms (*E*) and (*Z*) (Figure 30.).

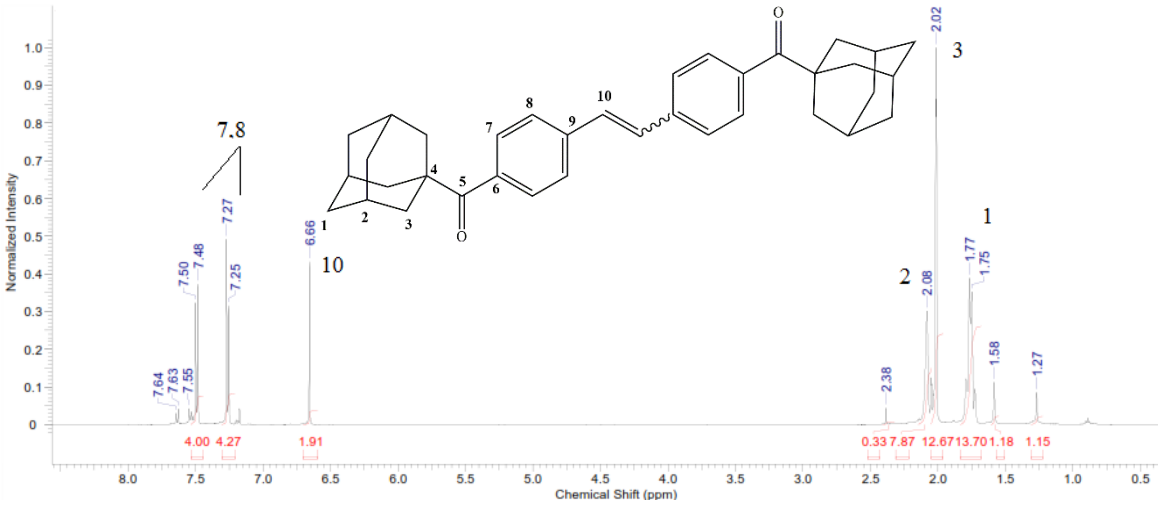
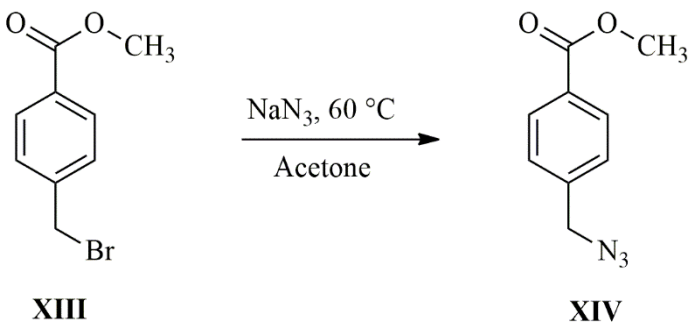


Figure 31. ^{1}H NMR spectrum of compound X

Subsequently, 1,2-bis(4-(1-adamantylcarbonyl)phenyl)-1,2-dibromoethane (**XI**) was prepared from compound **X**. Bromine was dissolved in chloroform and then carefully added by syringe with stainless steel needle, drop by drop. Whole reaction process was monitored by alumina matrix TLC (SiO_2, PE:EA=4:1, v:v). Sodium thiosulfate was used for to neutralize unreacted bromine. Finally, white powder was obtained and structure was proved by NMR.

Compound **XII**, 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne, was prepared from compound **XI** by dehydrobromation. The reaction was fast and completed within 3 h but purification process was complicated. Separation was achieved by column chromatography (SiO_2, $CHCl_3$:PE=1:1, v:v) and product was obtained in three different fractions together with other compounds. Therefore, it was necessary to separate every fraction individually to get pure compound **XII**. Compound **XII** was identified by NMR and it was starting material for the model reaction that is was described in my bachelor thesis.

Before abovementioned model reaction was applied, it was necessary to prepare methyl 4-(azidomethyl)benzoate **XIV** from methyl 4-bromobenzoate **XIII**. Reaction itself was finished in 1 hour, and purification was then performed by column chromatography in mobile phase ($CHCl_3$:PE=1:1) to obtain the compound **XIV** in yield of 94 %. Compound **XIV** was identified by GC-MS.



XIII **XIV**

Figure 32. Synthesis of methyl 4-(azidomethyl)benzoate

Attempting the performation of cycloaddition of compound **XII** with organic azide (**XIV)**, three different reaction conditions were tested (Figure 32.). Reaction with 4-(azidomethyl)benzoate (**XIV**) was supposed to give N-1or N-2 substituted triazole. The first reaction, presented on the (Figure 32) was monitored by TLC for the five days without any changes. The reaction temperature was increased to 150 °C after five days, as CuAAC is highly dependent on temperature. Unfortunately, no changes have been observed. Sodium azide and cooper iodine were used in different concentrations in second and third case.

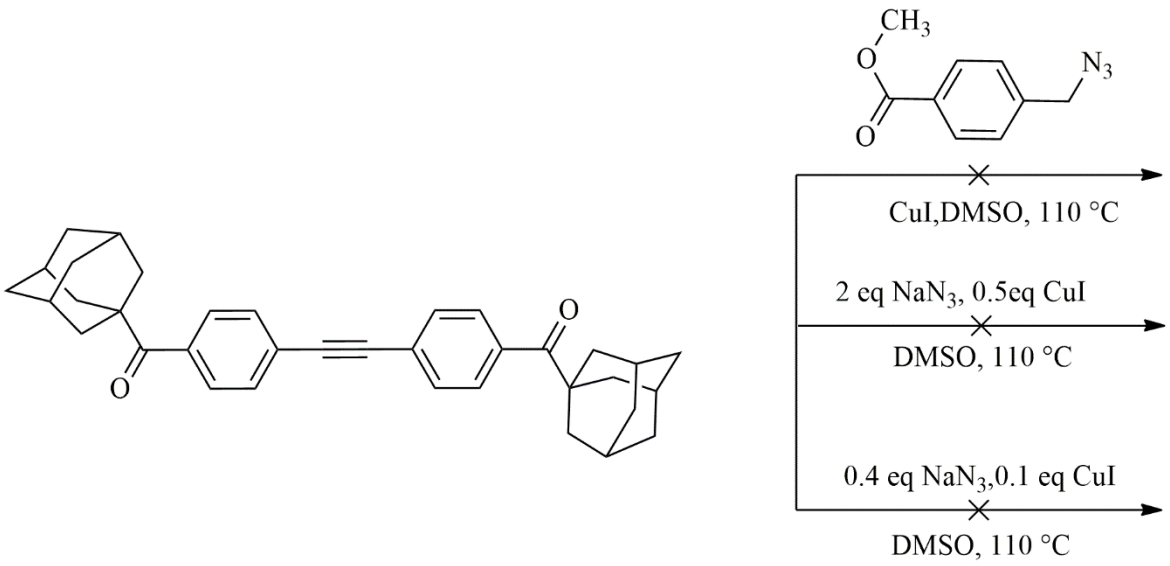


Figure 33. Reaction of compound (XII) with azides

Both reactions were monitored for five days and the reaction temperature was again increased to 150 °C in an aim to initiate reaction. Again, no changes were observed. The reason why reaction was not initiate could be caused by CuI as a catalyst. As compound **XII** wasn't absolutely pure after so many steps of preparation, this could be cause of inhibition of CuAAC.

4.2 Synthesis of ethyl diazoacetate

Ethyl diazoacetate was prepared by diazotation. Our aim was to use it the next step in reaction with the compound **XII** and to initiate cyklopropenation reaction. Synthesis of ethyl diazoacetate was performed under conditions that are described in Figure 33.

As ethyl diazoacetate is toxic and known as potential explosive substance, manipulation

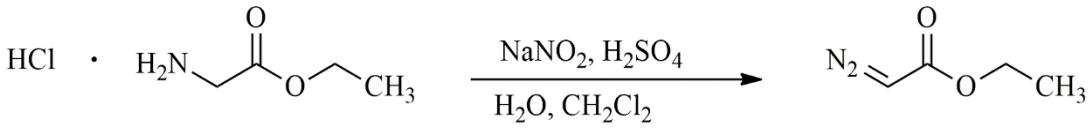


Figure 34. Preparation of ethyl diazoacetate

was made in well-ventilated hood. This method uses methylene dichloride to protect ethyl diazoacetate from potential decomposition caused by aqueous mineral acid. Additionally, temperature control during reaction was one of key points because decomposition could be also caused by higher temperature. That's why it was necessary to perform neutralization of sulfuric acid with 5% sodium bicarbonate solution, before ethyl diazoacetate was concentrated. Efficient separation of dichloromethane was indicated by the absence of yellow color in the distillate. Prepared ethyl diazoacetate is unstable compound, therefore was stored at –8 °C in dark brown flask.

4.3 Model reaction of diphenylacetilene and ethyl diazoacetate

Figure 34 shows four model reactions exanimated with aim to select best catalyst and temperature. During this examination, methylene dichloride was used in all cases as a solvent at room temperature with catalyst $Rh(OAc)_4$, $Cu(I)(CH_3CN)_4PF_6$ and copper. Additionally, reaction was repeated with copper(0) catalyst at 40 °C. Duration for each reaction was 9 h. Reactions were monitored by GC-MS and no final purification has been performed after reactions finished. $Cu(I)(CH_3CN)_4PF_6$ with 33.93 % and $Rh(OAc)_4$ 39.86 % were lowest efficient catalysts according to GC-MS reports. Best result showed copper at room temperature 77.31 %. The same reaction was repeated at 40 °C, which led to yield increase up to 81.62 %.

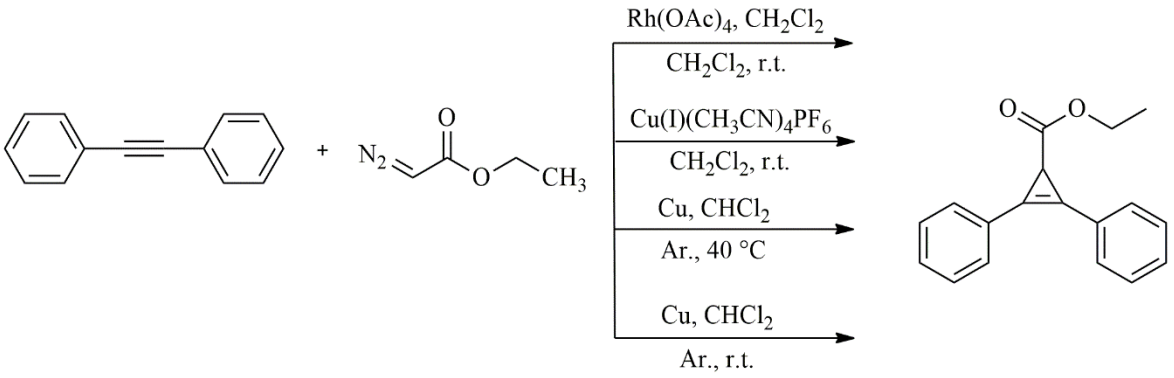


Figure 35. Model reaction of diphenylacetylene and ethyl diazoacetate

4.4 Synthesis of ethyl 2,3-bis(4-(adamantane-1-carbonyl)phenyl)cycloprop-2-enecarboxylate

The reaction of compound **XII** and ethyl diazoacetate was performed with the previously selected catalyst. According to the literature, copper showed as the best catalyst for this type of recation. Therefore, was studied the influence of Cu^0 as well as his complexed form, despite the fact that showed low efficiency in model reaction. 2,3-Bis(4-(adamantane-1-carbonyl)phenyl)cycloprop-2-enecarboxylate (**XV**) was prepared at 140 °C, under argone atmosphere and in xylene as a solvent. Reaction progress was monitored by TLC and three spots appeared after 10 h of reaction (Figure 35). Product purification has been done by column chromatography. In second reaction $Cu(I)(CH_3CN)_4PF_6$ was used, at room temperature for 10 h. After purification, each isolated fraction was analyzed by NMR. Unfortunately, any of isolated fraction for both reactions, have not proved expected structure **XV**.

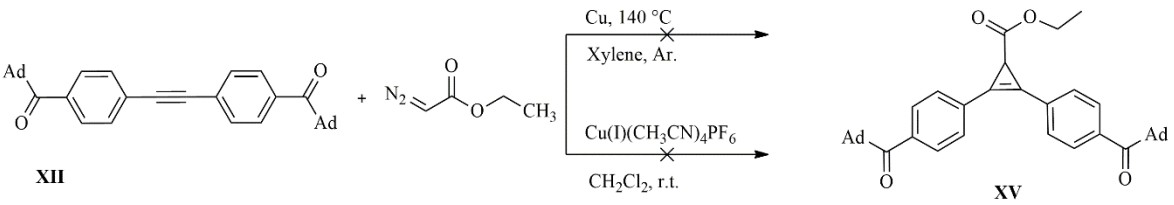


Figure 36. Preparation of compound **XV**

CONCLUSION

In this research, model reaction for preparation of ditopic ligands for supramolecular systems, which bears two adamantans and carboxylic group, was applied. Adamantane-1-carboxylic acid was chosen as a starting compound, which was treated in following reaction sequence: nucleophilic substitution, Grignard reaction, radical bromination, Wittig reaction, electrophilic addition, and, finally, elimination to give 1,2-bis(4-(1-adamantylcarbonyl)phenyl)ethyne.

On the ethyne as a key intermediate, it was initially studied 1,3-dipolar cycloaddition in the presence of CuI and under different reaction conditions. Desired differently substituted 1,2,3-triazole was not detected in the reaction mixtures under tested conditions. After this, reactions of ethyne and ethyl diazoacetate with Cu and $Cu(I)(CH_3CN)_4PF_6$ as a catalysts were studied for preparation of cyclopropane derivate. Unfortunately, cyclopropane derivate was not obtained in any of mentioned reactions.

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LIST OF ABBREVIATIONS

BPO	benzoyl peroxide
CuAAC	copper catalyzed azide-alkyl cycloaddition
DEE	diethyl ether
DIEA	*N*,*N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
EA	ethyl acetate
GC-MS	gas chromatography - mass spectrometry
NBS	*N*-bromosuccinimide
PE	petroleum ether(40–60 °C)
TLC	thin-layer chromatography
r.t.	room temperature

LIST OF FIGURES

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