Synthesis of Supramolecular Components Based on the Adamantane and 1,2,3-triazole

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Bachelor thesis
2013

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Fakulta technologická
Ústav technologie potravin
akademický rok: 2012/2013

ZADÁNÍ BAKALÁŘSKÉ PRÁCE
(PROJEKTU, UMĚLECKÉHO DÍLA, UMĚLECKÉHO VÝKONU)

Jméno a příjmení:	**Stefan ŽIVANOVIC**
Osobní číslo:	**T100031**
Studijní program:	**B2901 Chemie a technologie potravin**
Studijní obor:	**Chemie a technologie potravin**
Forma studia:	**prezenční**
Téma práce:	**Syntéza supramolekulárních komponent na bázi adamantanu a 1,2,3-triazolu**

Zásady pro vypracování:

I. Teoretická část

1. **Obecné vlastnosti triazolů**
2. **Rovnovážné chování 1H a 2H triazolů**
3. **Metody přípravy triazolů se zvláštním ohledem na předchozí bod**

II. Praktická část

1. **Příprava výchozích látek**
2. **Studium modelových reakcí vedoucích k 2,4,5-trisubstituovaným triazolům**
3. **Příprava cílových trisubstituovaných triazolů s adamantanovými substituenty**

Rozsah bakalářské práce:

Rozsah příloh:

Forma zpracování bakalářské práce: **tištěná/elektronická**

Seznam odborné literatury:

[1] MCMURRY, John. Organic chemistry. 6th ed. Belmont, CA: Thomson-Brooks/Cole, c2004, 1 v. (various pagings). ISBN 05-343-9001-3.
[2] HARWOOD, Laurence M, Christopher J MOODY a Jonathan M PERCY. Experimental organic chemistry: standard and microscale. 2nd ed. /. Malden, MA: Blackwell Science, 1999, x, 716 p. ISBN 06-320-4819-0.
[3] KOVÁČ, Jaroslav, Alžbeta KRUTOŠÍKOVÁ a Rudolf KADA. Chémia heterocyklických zlúčenín. Bratislava: VEDA, 1982.

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Ústav chemie

Datum zadání bakalářské práce: **16. ledna 2013**

Termín odevzdání bakalářské práce: **2. května 2013**

Ve Zlíně dne 4. února 2013

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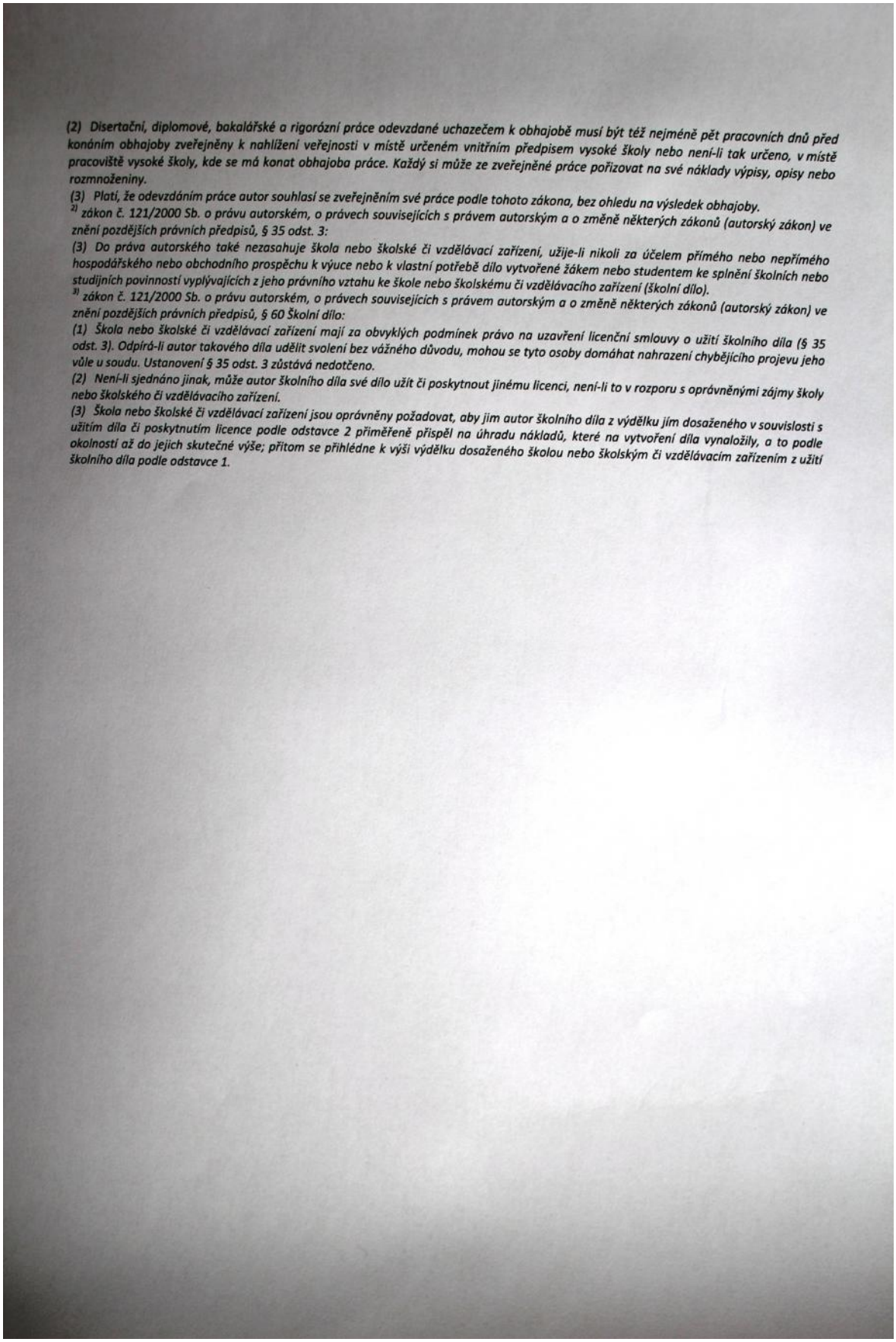

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ABSTRAKT

Czech abstract

V této práci byla zkoumána modelová reakce pro syntézu supramolekulárních komponent na bázi adamantanu a 1,2,3-triazolu. Za tímto účelem byly, za využití 1,3-dipolarní cykloadice, radikálové bromace, esterifikace, a nukleofilní substituce, připraveny dvě sloučeniny 6-(4,5-difenyl-2*H*-1,2,3-triazol-2-yl)hexanová kyselina a methyl-4-((4,5-difenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoát, jakožto modelové látky pro další syntézu. Mezi technikami používanými k identifikaci připravených produktů byly GCMS, ^{1}H NMR, ^{13}C NMR, ESI-MS a HPLC. NMR výsledky ukázaly, že alifatický methyl-6 bromohexanoát reagoval v poloze 2 triazolového sdkeletu za vzniku symetrického produktu, zatímco methyl-4 bromomethylbenzoát poskytl produkt nesymetricky substituovaný v poloze 1.

Klíčová slova: 1,3-dipolarní cykloadice, nukleofilní substituce, N2-substituovaný 1,2,3-triazol.

ABSTRACT

English abstract

In the present research, a model reaction for the synthesis of supramolecular components based on the adamantane and 1,2,3-triazole was investigated. For this purpose 1,3-dipolar cycloadition, radical reaction, esterification, and nucleophilic substitution were used to preparate 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 as model compound for future synthesis. Among the technics used to identify the compounds were GCMS, ^{1}H NMR, ^{13}C NMR, ESI-MS and HPLC. NMR results showed the aliphatic methyl 6-bromohexanoate substituted starting triazole at position 2 to form a symmetrical product, whereas methyl 4-bromomethylbenzoate gave final triazole derivate non-symmetrical substitution at position 1.

Keywords: 1,3-dipolar cycloadition, nucleophilic substitution, N2-Substituted 1,2,3-Triazole.

ACKNOWLEDGEMENTS

I am deeply grateful to Mgr. Robert Vícha, Ph.D. for sharing his knowledge, experience, time and dedication during my bachelor research. I would to express my gratitude also to Ing. Babjaková Eva and Ing. Branná Petra, for their help with assistance with experiments and GCMS measurements. Additional thanks goes to Ing. Lenka Fojtíková and Ing. Michal Rouchal, Ph.D. for helping me with HPLC analysis.

Contents

INTRODUCTION

General properties

The 1,2,3-triazole is a heterocyclic compound with three nitrogen atoms within the ring. Reaction of 1,2,3-triazole heterocyclic system have been known since the 19th century. The triazole ring also can contain another heteroatom (for example sulfur or oxygen). A typical example of this group is the 1,2,3-triazole, also called v-triazole, ,,v" means a vicinal. Arrangement of the three nitrogen atoms within a ring of heterocyclic compound as can be seen in Figure 1.

Even that triazole compound are known for more than 100 years, no 1,2,3-triazole has not been isolated from any natural compounds[1]. However now days, thousands of articles and reviews about synthesis of 1,2,3-triazole are available in different databases. Actually, it is almost impossible to imagine some field of chemistry in which this powerful compound is not used, including biochemistry, pharmacy and drug industry [2-4].

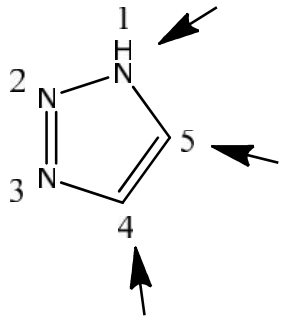


Figure 1. Structure of 1,2,3-triazole positions available for substitution

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 stabile 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 at the same time it could also take part in hydrogen bond formation as well as in dipole–dipole and π…π stacking interactions[6].

Tautomer forms of 1,2,3-triazole

As can be seen in Figure 2, the 1,2,3-triazole could appear in three tautomer forms but two of them are identical.

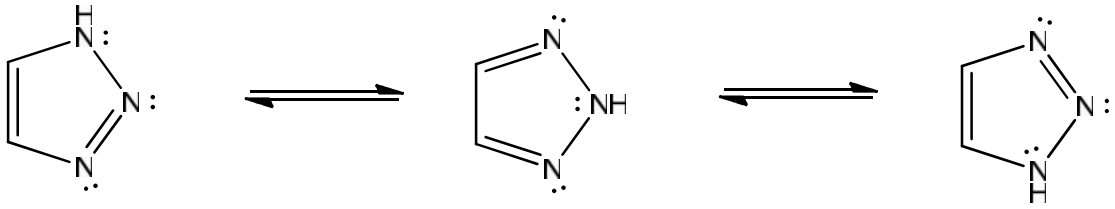


Figure 2. Tautomer forms of the 1,2,3-triazole.

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 solution and at lower temperatures, the molecules in 1H-forms are associated via intermolecular H-bounds[7].

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. Nevertheless in the case that a proton is replaced by some bigger group, that will stay fixed and no group shift will occur[7].

Acid basic properties

The 1,2,3-triazole belong to the group of weak base. The pK_b of 1,2,3-triazole is 1.17 that makes this triazole to be less basic than pyrazole. However, the unsubstituted nitrogen triazole atom will occure as NH-acid. The acidity of 1,2,3-triazole with a pK_a value of 9.3. This is in general due to the continued delocalization of the negative charge in the conjugate base[7].

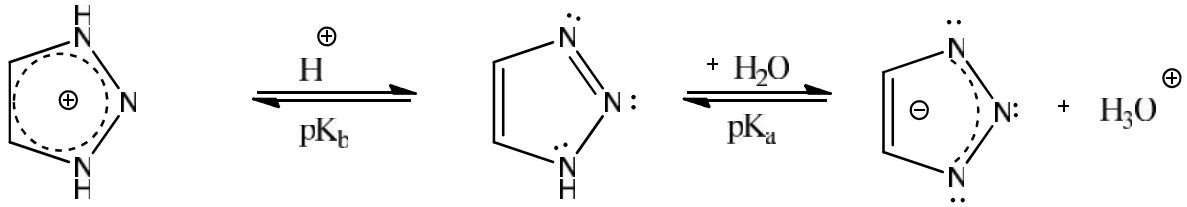


Figure 3. Acidobasic behavior of the 1,2,3-triazole

I. THEORY

1 SYNTHETIC STRATEGIES

1.1 Click Chemistry

„Click chemistry" was for the first time discovered and used firstly by Linus Pauling in 1933[8]. But the first scientist who described "Click chemistry" was K. B. Sharpless in 2001. Basic principle of "Click chemistry" method is to generate substances quickly and reliably by joining small units together. "Click chemistry" does not present some specific reaction it is just a concept which mimics nature. Utilizing of "Click chemistry" are pretty easy to achieve and give intended products in very high yields mostly without byproducts or with very small yields of byproducts. This powerful and characteristic method has demonstrated to work properly under several conditions.

Organic azides and terminal alkynes are transformed by the copper-catalyzed reaction into 1,4-disubstituted 1,2,3-triazoles. Catalyzed reaction will transform terminal alkynes and organic azides completely into 1,4-disubstituted 1,2,3-triazoles, instead of uncatalyzed reaction which by high temperature provides mixtures of 1,4- and 1,5-triazole regioisomers[9]. Before the discovery of copper catalyzed reactions it had been published more than 7000 1,4-disubstituted 1-H-1,2,3-triazole compounds[10]. Reaction had been described by a set of tight criteria. ‘‘

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.’’

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 presented in Figure 4.

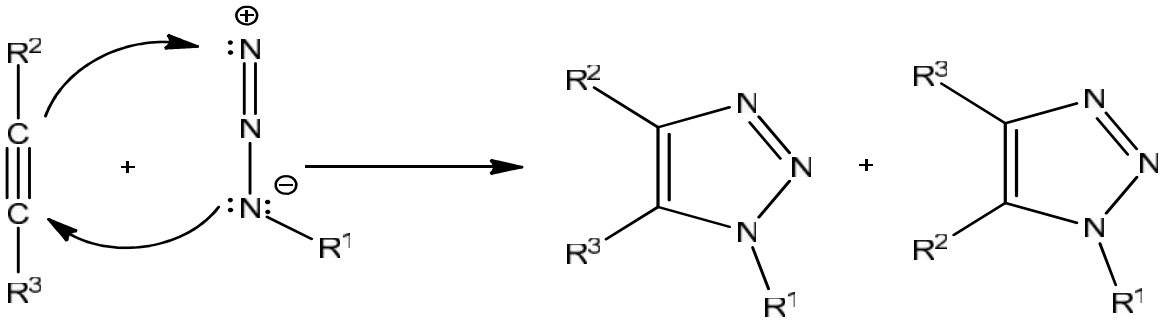


Figure 4. 1,3-Dipolar Cycloaddition toward the triazole ring

The 1,3-dipolar cycloadittion is highly similar to Diels-Alder reaction both groups belong to pericyclic reactions. This pericyclic reaction is very characteristic and considera-ble for the synthesis of heterocycles and conversion 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 (ie. 4π + 2n and 6 π respectively). The dissimilarity lays in that three atoms supply the four electron instead of four atoms in a Diels-Alder reaction and thus 1,3-dipolar cycloadition leads to 5-memberd ring whe . The result of a wide range of cycloaddition reactions including the 1,3-dipolar cycloadittion is that they proceed with high stereocontrol[11].

The evolution of the 1,3-dipolarcycloaddition started 100 years ago, during this century, different 1,3-dipoles have been discovered. Several scientist 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. After describing the mechanism of the 1,3-dipolar cycloaddition, one of the most important features 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 described in figure 5.

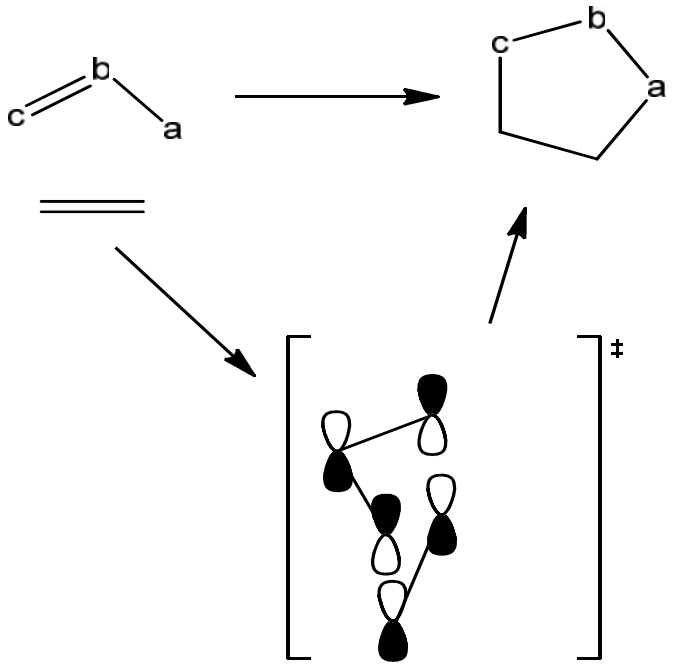


Figure 5. Description of c-b-a structure

1,3-dipoles can be separated into two groups: 1) The allyl anion type which is typify by four electrons in three parallel p_z orbitals vertical to the plane of the dipole and the curved 1,3-dipole.

Figure 6. shows the two resonance structures where the three centers 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.

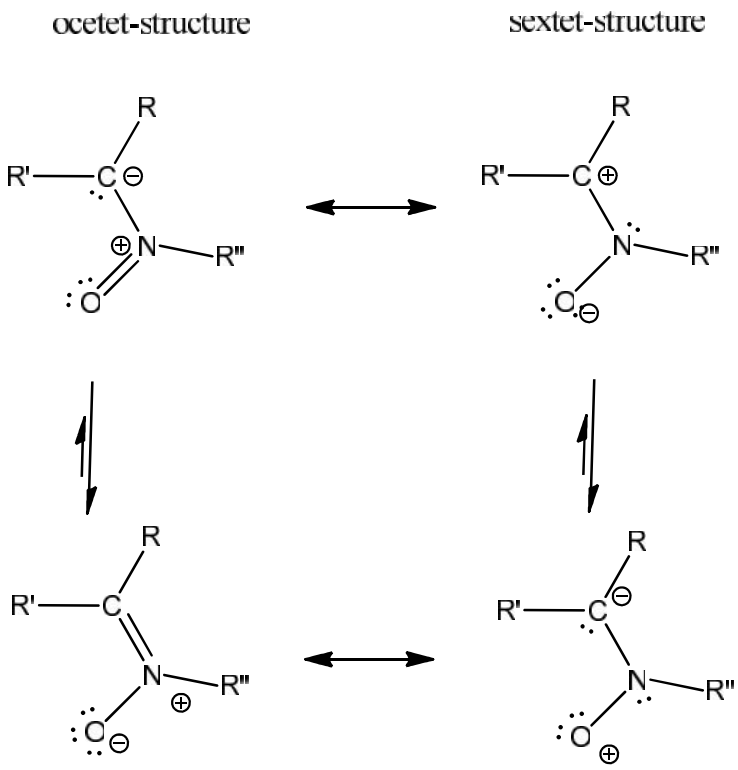


Figure 6. Allyl anion type

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

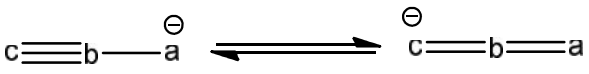


Figure 7. Propagyl/allenyl anion type

Figure 7. presents a propargyl/allenyl anion type, but as can be seen, the form is linear and 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 8.

Figure 8. Hypervalent representations

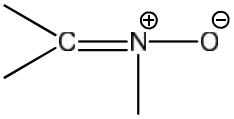
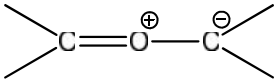
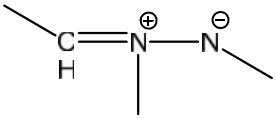
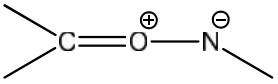
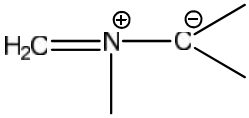
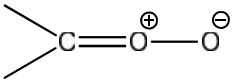
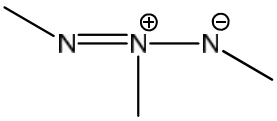
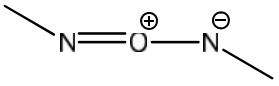
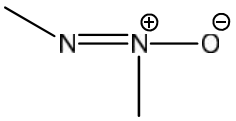
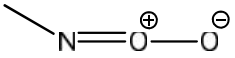
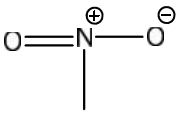
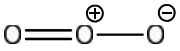
The presents of 1,3dipoles is characteristic in elements from main group IV,V and VI. Because the 1,3-dipoles are structured from elements of the second row, and according to literature there is a limited number of possibilities that can be formed by a change of nitrogen, carbon, and oxygen on the central atom of the dipole[12].

Very few articles have been published with sulfur and phosphorus incorporating 1,3-dipoles. The classification of two types of 1,3-dipole are draw in Table 1.

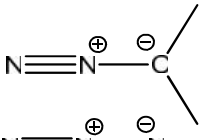
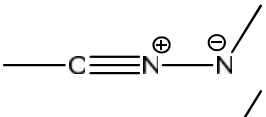
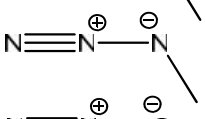
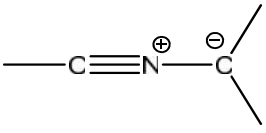
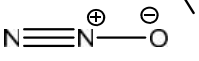
Table 1. Classification of the parent 1,3-Dipoles

Classification of the Parent 1,3-Dipoles

Allyl anion type

Nitrogen in the middle		Oxygen in the middle	
	Nitrones		Carbonyl Ylides
	Azomethine Imines		Carbonyl Imines
	Azomethine Ylides		Carbonyl Oxides
	Azimines		Nitrosimines
	Azoxy Componds		Nitrosoxides
	Nitro Componds		Ozone

Propargyl/allenyl anion type

Nitrillium Betaines		Diazonium Betaines	
	Nitrile Oxides		Diazoalkanes
	Nitrile Imines		Azides
	Nitrile Yildes		Nitrous Oxide

2 RECENT EXAMPLES

It is possible to classify this broad number of synthetic methods 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 depicited in Figure 9[13]. We will be focused on the results that were published during the last five years.

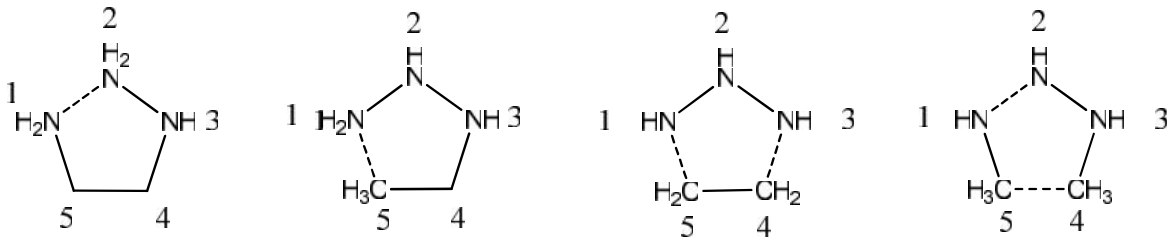


Figure 9. Synthetic methods of 1,2,3-triazole

2.1 Copper-Catalyzed Azide-Alkyne Cycloaddition Reaction in Water Using Cyclodextrin as a Phase Transfer Catalyst

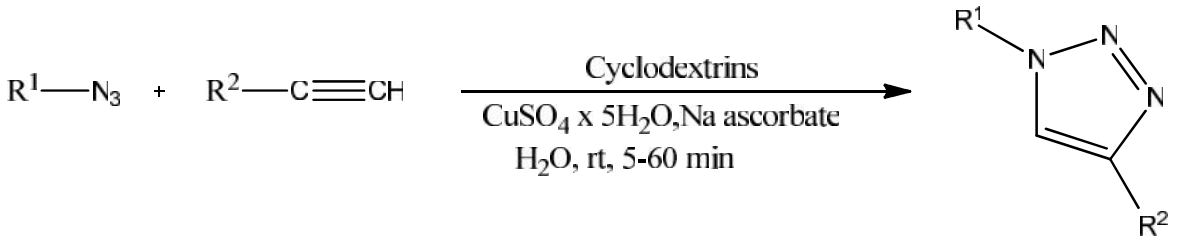


Figure 10. Synthesis in Cyclodectrin

The synthesis of 1,4-disubstituted-1,2,3-triazole from azid and terminal alkynes is possible in aqueous solution with different types of cyclodextrine.

Jung and Yeong reported that β-cyclodextrin plays an important role in the effective phase transfer within CuAAC reaction using water as a solvent.

In the absence of cyclodextrin and after one hour of reaction at room temperature, 40.5 % of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (3b) was obtained. After 4.5 hours, the reaction was completed to yield of 99.5 % of the product 1-benzyl-4-phenyl-1*H*-1,2,3-triazole.

The three dissimilar types of cyclodextrins in all reactions provide almost the same yield but because of the price autors chose β-cyclodextrin as the cheapest one. Using β-cyclodextrin, the conversion to triazole was quick. However, lower yield was obtained 78%. The problem was that the product 1-benzyl-4-phenyl-1*H*-1,2,3-triazole formed a water-soluble inclusion complex in aqueous media.

To skip this problem, the amount of β-cyclodextrin was reduced from 10 to 2.5 mol %. After 15 minutes of reaction, the obtained yield was 96 %. Furthermore and a reduction of β-cyclodextrin molar percentage from 2.5 to 1 mol % prolonged the reaction time to 30 minutes and isolated yield was 97 % [14].

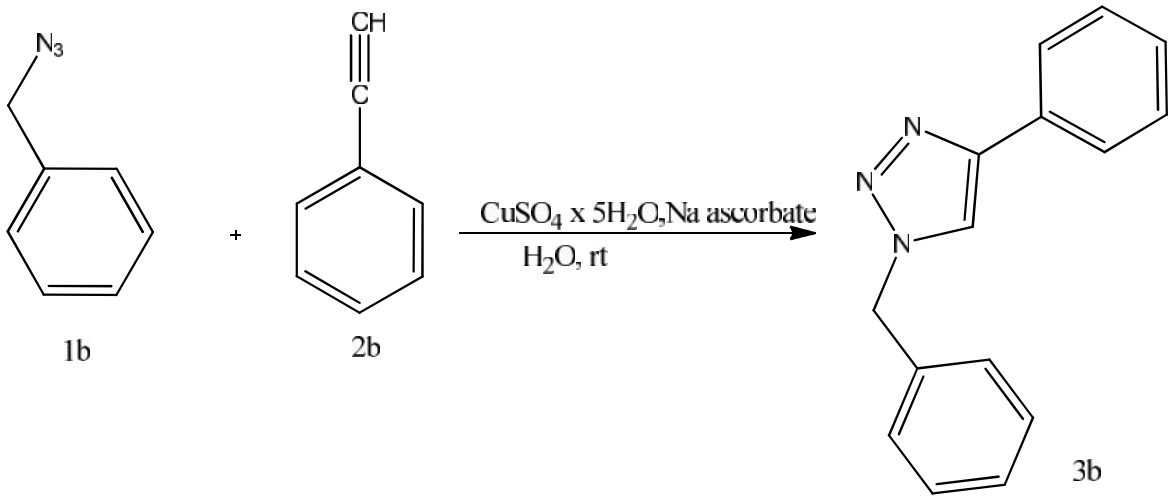


Figure 11. CuAAC of triazole in cyclodextrin

Table 2. Cyclodextrin effects on Cu-catalyzed [2+3] cycloaddition Azide 1b with alkyne 2b

entry	additive (mol%)	reaction time	conversion (%)[a]
1		1h	40.5
2		5.5h	99.5
3[b]	β – CD (10)	10 min	100
4	α – CD (10)	10 min	100
5	γ – CD (10)	10 min	100
6[c]	β – CD (2.5)	10 min	93.3
7[d]	β – CD (1)	10 min	82.2

[a]Conversion yield was monitored by ^{1}H NMR. [b]Isolated yield was 78%. [c]The conversion to triazole 3b was completed after 15 min. After workup, isolated yield was 96%. [d]The conversion to 3b was finished after 30 min. After workup, isolated yield was 97%.

2.2 Ultrasound and microwave synthesis of 1,2,3-Triazole

Synthesis of 1,2,3-Triazole with Cu as the catalyst was proved by ultrasound and microwaves synthesis. The main role of ultrasound is the mechanical depassivation and the increment of both, electron and mass transfer from the metal to the organic acceptor. In click synthesis**,** a wide range of 1,4-disubstituted 1,2,3-triazole has been prepared applying ultrasound and microwaves.

Copper as metallic catalyst, is the best choise because of the price in comparison with other solid catalysts. The use of water solutions has the advantage of metal waste removal due to the fact that the water acts as a ligand. Ultrasound is used to activate the hard metal surface and this method is known for having a cleaning impact of ultrasonic waves. The result is to provide a depassivated surface where the reaction components can interact. Furthermore the ultrasound can improve the diffusion of the reagent from the solution to the metal surface. In addition, the electron transfer from the activated surface to the reducible part of the organic substrate is facilitated. Finally a soluble product is generated after the extraction of an ion from the surface. Apparently, cavitational energy

created by increasing and forcible collapse of microbubbles releasing amount of kinetic energy wich is enough to drive the process till the end.

Another fast and easy way to synthesize 1,2,3-triazole is by means of microwave synthesis. Under mild conditions with cycloadition reaction of alkyl azides and thermal alkynes and using Cu(I) as catalyst, high yield of isolated product and regioselectivity was obtained[15].

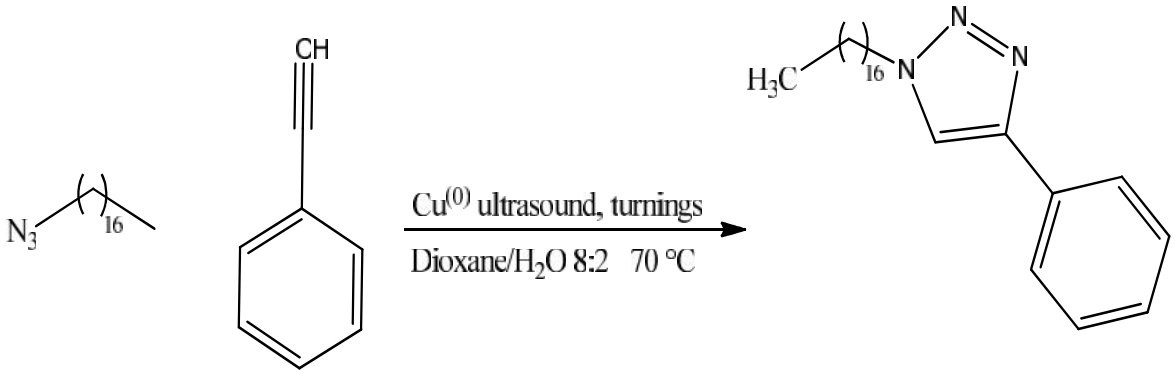


Figure 12. Ultrasound synthesis of triazol

2.2.1 Cavitation energy

Cavitation is the term which defines and explains a process of fast microbubles growth in aqueous solution with high negative pressure. Compression cycle is followed by a microcavities collapse and releasing of kinetic energy strong enough to brake the chemical bond. Concomitant shocking of waves and shear forces are liable for mechanical effects. The best model proposes the local temperatures exceeding 5,000 K and pressures of several thousand atmospheres during the collapse. In addition, considerable cooling rates (> 10^{10} K s^{-1}) are generated, and therefore cavitation can be considered as quasi-adiabatic process. Different molecules hitted with bubbles will rather sustain excitation and homolytic cleft, and on the end delivered to the medium in radical form. Ultrasonic energy after entering in the chemical system is strongly dependent on the physical characteristics of the medium like viscosity, temperature (i.e. vapor pressure), and surface tension of the solvent[15].

2.3 Microwave synthesis

Wavelengths of microwaves are between 1 mm – 1 m with related frequencies between 0.3 and 300 GHz. The application of microwave technology in organic chemistry started in the 1980s. Basically, the most important characteristic in microwave synthesis is the short reaction time and expanded reaction range. Microwave radiation can appears as two separated components (electric and magnetic fields). Dielectric heating is resulted by two main mechanisms: dipolar polarization and conduction[16].

2.3.1 Conduction mechanism

The influence of an electric field is that ions or even a single isolated ion with hydrogen bond will move through the solution. This will result in waste of energy by increasing collision rate and converting kinetic energy to heat. The main difference between conductivity and dipolar mechanisms is that the conductivity mechanism has a stronger interaction.

In the work with reflux system there is small risk of explosions but if the system is at atmospheric pressure and temperature, the combustible vapor cannot be released into the cavity of the microwave[16].

2.3.2 Dipolar polarization

Dipolar polarization mechanism is based on the dipole moment of molecules which is main condition for a substance to produce heat. A dipole is very sensitive to external electric fields. This dipole will try to align itself with the field by rotation. Absorption of molecules will strongly depend on the frequency and viscosity of the environment[16].

Product 2-(5-phenyl-2*H*-1,2,3-triazol-4-yl)benzonitrile was obtained by the reaction of 2-(phenylethynyl)benzonitrile with 5 equiv of sodium azide in DMF at 80 °C, in the yield of 98 % after 6 days. Increasing of amount of sodium azide to 10 equiv didn't make reaction faster.

By using microwave irradiation with 75 W source and at temperature of 140 °C, rection was repeated but with 1,5 equiv of sodium azide and in dimethyl sulfoxide. After 10

minutes, product 2-(5-phenyl-2*H*-1,2,3-triazol-4-yl)benzonitrile was obtained in 98 % yield[17].

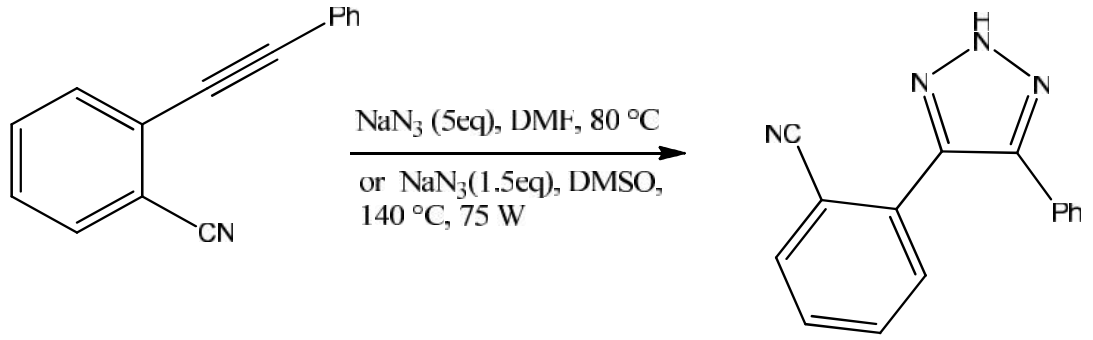


Figure 13. Synthesis of 4,5-disubstituted-2*H*-1,2,3-triazole

2.4 Highly regioselective N-2 arylation of 4, 5-dibromotriazole

Wang, et al., obtained the compound 2-aryl-4,5-dibromotriazole with high regioselectivity by direct N-2 arylation using 4,5-dibromo-1,2,3-triazole as a nucleophile. A single isomer (4,5-dibromo-2-(2-nitrophenyl)-2*H*-1,2,3-triazole) was obtained with higher yield (96%) by aromatic substitution of 4,5-dibromotriazole this was achieved by treatment of 4,5-dibromo-1,2,3-triazole with 2-fluoronitrobenzen in DMF with K_2CO_3 for one hour at 70 °C as can be seen in figure 14.

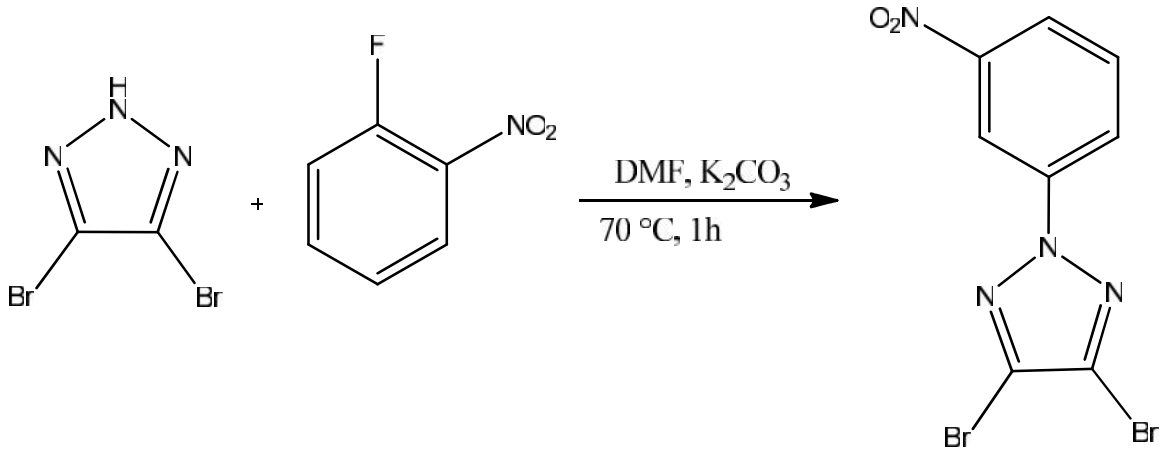


Figure 14. Aromatic substitution of 1,5-dibromotriazole

Following procedure involved the debromination of the triazole to obtain a 4,5-unsibstituted triazole. High yield 96 % was obtained under H_2 with 10% Pd/C in methanol as described in Figure 15. The efficient synthesis of 2-aryltriazoles was achieved by providing steric hindrance and influenced electron density to decrease the reactivity of N-1 and N-3 positions[18].

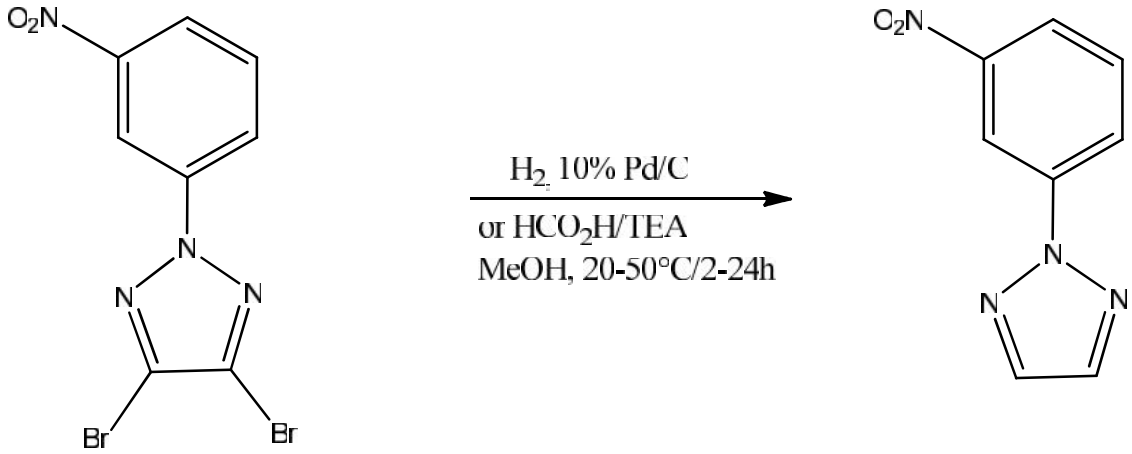


Figure 15. Reduction of dibromotriazoles by hydrogenation

2.5 Regioselective synthesis of cannabinoid receptor

The regioselective synthesis of 4-Alkoxycarbonyl-1,5-diaryl-1,2,3-triazole and further application as CB1 cannabinoid receptor was described by Shu and coauthors. Click chemistry was used to construct the 1,2,3-triazole ring system and to provide suitable intermediates for parallel synthesis of different analogues. The triazole was incorporated into to the vicinal diaryl group (1,5-diaryl-1,2,3-triazole) in order to facilitate the interaction with a unique region of the CB1 receptors. The first step consisted in the conversion of 4-chloroaniline (1) into azide with triflyl azide (89% yield) (2), followed by the formation of an intermediate (1,5-diaryl-1,2,3-triazole-4-magnesium chloride) (4) by reaction of 4-chloracetylene (3) with the azide. Reaction of the intermediate with 1N NH_4Cl gives product 1-(1,5-bis(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethanone 85% yield (4b) and the reaction of methyl chloroformate with the intermediate gives product 1-(1,5-bis(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)ethanone 67% yield (4a)[19].

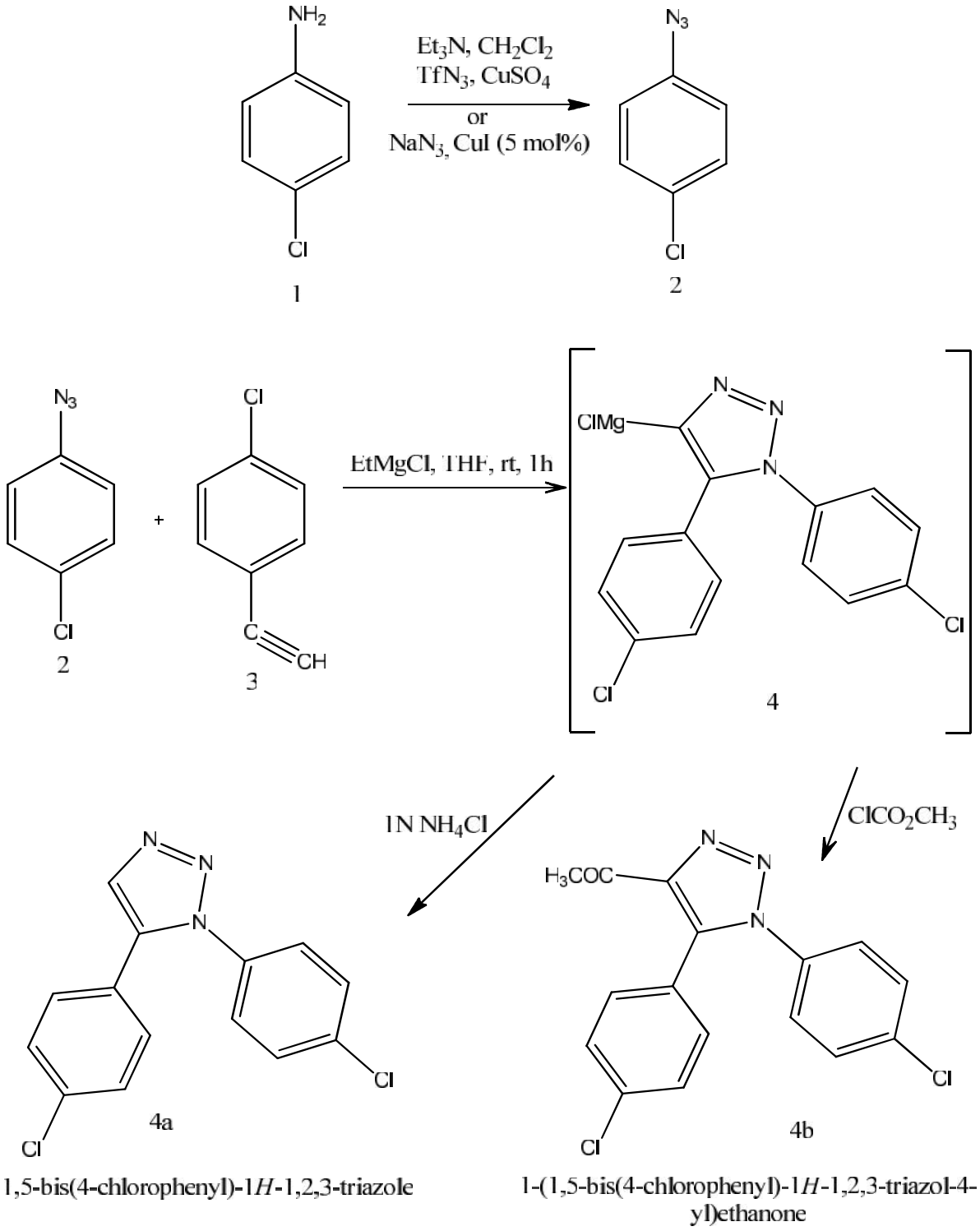


Figure 16. Synthesis of cannabinoid receptor

2.6 Ruthenium catalyzed cycloaddition of alkynes and organic azides

Other method of cycloaddition alkynes and organic azides is catalyzed with ruthenium. This method of catalytic conversation of alkynes influenced with ruthenium complex is well known, for the intermediacy of ruthenium complex (II) acetylide, vinyliden, and ruthenametallacyclic complexes had been provided. Reaction is also investigated with benzyl azide and phenylacetylen in the presence of ruthenium complex. Finally, product was 1,4-disubstituted triazloes with low amount of dimmers and oligomers of phenylacetylen[20]. During investigation of the catalytic activity of different ruthenium complexes in reaction of aliphatic azides and alkynes, it have been found that pentamethyl-cyclopentadienyl ruthenium(II) chloride tetramer $[Cp^*RuCl]_4$ in dimethylformamide appeared to be significantly better than $Cp^*RuCl(PPh3)_2$ in most other solvents[21].

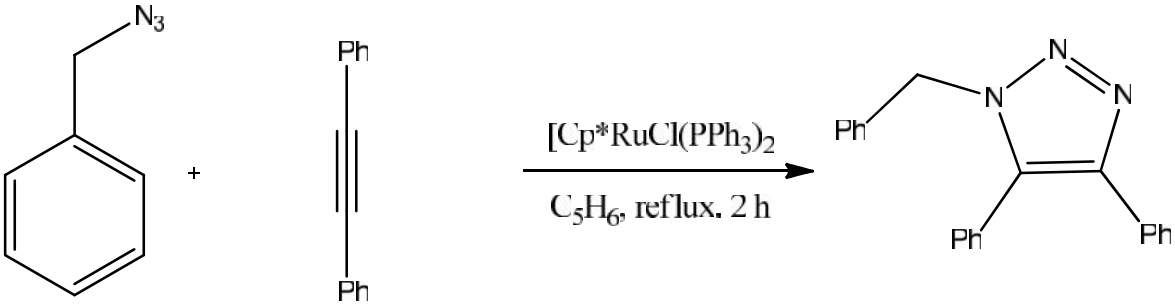


Figure 17. Ru-catalyzed synthesis of triazole from alkynes

2.7 Triazole Applications in Biology and Nanotechnology

The importance of the use of triazole ring in nanotechnology was demonstrated by El-Sagheer and Brown. They proposed the synthesis of triazole DNA in order to give special characteristics to the new oligonucleotides formed by click ligation, namely. The biocompatibility of the new modified DNA was tested on *E. coli* [22].

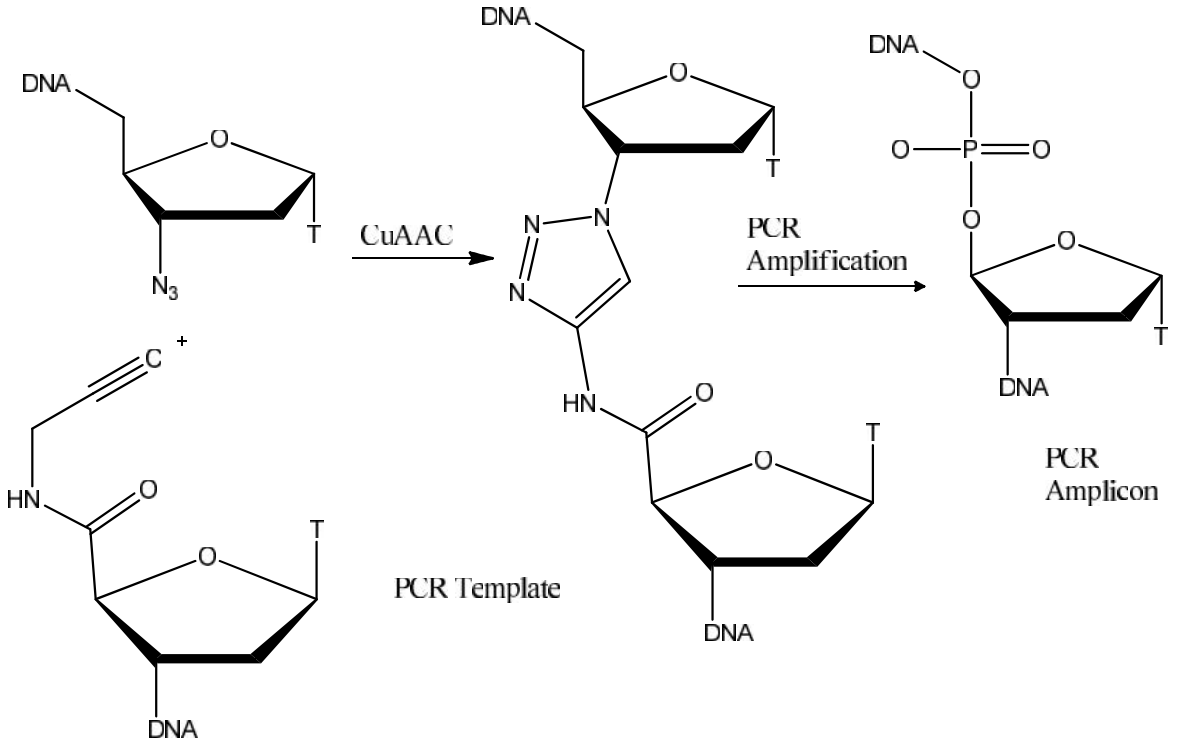


Figure 18. Synthesis and PCR amplification from the first generation triazole DNA backbone linkage.

Triazole-linked DNA one more time proved the stability of triazole ring. Synthesis of triazole ring have been reviewed in huge range of publications in last few decades. A lot of different methods and ways to synthetize this molecule have been proved. But one of most used ways is click reactions of CuAAC (copper-azide-alkyn-cycloadition). CuAAC was proved as reliable, simple and in wide scale applied way of making covalent bonds between building blocks also including a bulky functional groups[23].

II. ANALYSIS

3 EXPERIMENTAL PART

3.1 General Experimental

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 (1H) and 75.77 MHz (13C). 1H- and 13C-NMR chemical shifts were referenced to the solvent signals (1H: δ(residual CHCl3) = 7.27 ppm, δ(residual [D5]DMSO) = 2.50 ppm, δ(residual [D4]methanol) = 3.31 ppm ; 13C: δ(CDCl3) = 77.23 ppm, δ([D6]DMSO) = 39.52 ppm, δ([D4]methanol) = 49.15 ppm). The IR spectra were recorded using KBr discs with a Mattson 3000 FT-IR instrument and vw̃as 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) column. Helium was used as the carrier gas in the constant linear flow mode (38 cm·s-1); the column was held at 100 °C for 7 min and than heated at 25 °C/min to 250 °C before holding for the required time. Only peaks with relative abundances exceeding 5% were listed. The electrospray mass spectra (ESI-MS) were recorded using an amazon X ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ion source. All experiments were conducted in the positive-ion polarity mode. The instrumental conditions used to measure the single bisimidazolium salts and their cucurbit[n]uril mixtures were different; therefore they are described separately. Single bisimidazolium salts: Individual samples (with a concentration of 500 $ng \cdot cm^{-3}$) were infused into the ESI source in methanol:water (1:1, v:v) solutions using a syringe pump with a constant flow rate of 4 $\mu l \cdot min^{-1}$.

3.2 Chemicals

Diphenylacetylene, sodium azide, tetrakis (acetonitrile) copper (I) hexafluorophosphate, dimethyl sulfoxide (DMSO), Copper (I) Iodide, *p*-tolyl acetic acid, methanol, $CaCl_2$, sulfuric acid, sodium hydrogen (NaH) (60 % in Mineral Oil), tetrahydrofurane (THF), potassium hydroxide (KOH), potassium carbonate (K_2CO_2) 6-Bromohexanoic acid, tetrachloro methane, *N*-bromosuccinimide (NBS), dibenzoyl peroxide (DBP), silica gel 60. were purchased from Sigma Aldrich (Czech Republic). 4-(bromomethyl)phenyl acetic acid was prepared for some other purpose and was used courtesy of Petra Branná.

3.3 Synthesis of 4,5 diphenyl triazole

In a round bottom flask 1.0008 g (5.61×10^{-3}mol) of diphenylacetylene was mixed with 0.546 g (8.93×10^{-3}mol) of sodium azide and with 0.1112 g (5.83×10^{-4}mol) of CuI, followed by the addition of 10mL of DMSO. The mixture was refluxed for 3 h. The mixture was added into crushed ice. After ice melting, the product changed its physical properties, from liquid to precipitant. The solid was filtered with suction. The solid recovered was dried at room temperature, while the liquid was washed 20 times with a mixture of $CHCl_3$:AcOEt (8:2) and 4 times with distilled water and once with solution of saturated NaCl. Water was removed using Na_2SO_4. Rotary evaporator was used to remove the solvent. The product obtained was purified using column chromatography with a mixture of chloroform:methanol (32:1) as a mobile phase. The solvent was removed with the aid of rotary evaporator and the 4,5 diphenyltriazole was obtained.

ESI-MS: 222.1, 1+[$M+H^+]^+$; 465.2, 1+[$2M+Na^+]^+$(m/z,z).

EI-MS: 50(7), 51(19), 62(5), 63(16), 64(7), 76(7), 77(23), 82(11), 83(7), 89(21), 91(24), 96(5), 103(7), 118(16), 164(5), 165(51), 166(14), 192(12), 193(16), 220(17), 221(100), 222(17), m/z (%).

IR: 3060(w), 3018(w), 2985(w), 2802(w), 1603(w), 1583(w), 1566(w), 1514(w), 1489(w), 1441(m), 1381(w), 1286(w), 1267(w), 1227(w), 1209(w), 1178(w), 1159(w), 1138(w), 1122(w), 1092(w), 1072(w), 1026(w), 999(m), 928(w), 910(w), 854(w), 781(w), 760(m), 728(w), 696(m), 688(m), 675(w), 561(m), 507(w), 496(w), cm^{-1}.

^{1}H NMR: δ: 7.4 (s, 6H); 7.6 (s, 4H); 11.5 (s, 1H), ppm.

^{13}C NMR: δ: 130.1, 129.1, 129.02, 128.9, 128.5, 77.5, 77.2, 76.9, ppm.

Melting point: 123-128 °C

R_f= 0.47 (CH:Cl_3:MeOH, 32:1, v:v)

3.4 Synthesis of methyl-4-methylphenylacetate

10.015 g (0.066 mol) of *p*-tolyl acetic acid was added to a mixture of 50 mL of methanol and 0.5 mL of concetrated sulfuric acid. The mixture was refluxed for 3h. The reaction progress was monitored using GCMS. After, two thirds of the volume was evaporated and 50 mL of diethyl ether were added to the remained mixture. The solution

was washed 3 times with a mixture of water saturated with diethylether. Organic portion was dried with Na_2SO_4. The final product was obtained by removing the solvent in vacuum.

EI-MS: 41(38), 42(11), 43(27), 55(14), 59(15), 69(32), 74(100), 87(15), 97(8), 129(8), m/z (%).

3.5 Synthesis of methyl 6-bromohexanoate

10.0914 g (0.051 mol) of 6-Bromohexanoic acid was added to a mixture of 50 mL of methanol and 0.5 mL of sulfuric acid. The reaction proceeded similarly as described for the synthesis of *p*-tolylacetic acid methyl ester.

EI-MS: 50(6), 77(15), 78(7), 79(10), 103(9), 104(5), 105(100), 106(9), 164(19), m/z (%).

R_f= 0.59 (CH:Cl_3MeOH, 32:1, v:v)

3.6 Synthesis of 4-(bromomethyl)phenyl acetic acid

Into flame dried 50 mL flask, 98mL of freshly distillated CCl_4 from P_2O_5 was added, followed by 9.58 mL of methyl-4-methylphenylacetate, 11.88 g (0.066 mol) of NBS, and 0.15 g (6.19×10^{-4}mol) of DBP. The components were stirred and heated up to 90 °C. Tungsten lamp was used to initiate the reaction. After one and half hour, 1.075 g of NBS was added. Then the reaction proceeded for 2 h. The mixture was filtered with suction. The solid was washed 3 × times with CCl_4. The solvent was separated from the product by using rotary evaporator and column chromatography was used for purification. The petroleum ether-ethyl acetate (8:1) was used as mobile phase. As stationary phase was used silica gel 60.

EI-MS: 51(13), 52(8), 59(13), 63(5), 77(20), 78(19), 91(12), 102(5),103(20), 104(66), 105(20), 121(22), 131(9), 163(100), 164(13), 183(5), 185(5), m/z (%).

^{1}H NMR: δ: 3.6 (s, 2H); 3.7 (s, 3H); 4.5 (s, 2H); 7.26 (m, 2H); 7.36 (m, 2H), ppm.

R_f= 0.35 (PE:EA, 8:1, v:v).

3.7 Synthesis of methyl 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoic acid

Removal of water was ensured by oven dried glass of a 55 mL round bottomed flask. Freshly distillated 3 mL of THF were injected to the flask, followed by the addition of 0.1105 g (4.99×10^{-4}mol) of 4,5 diphenyl triazole, 0.09528 mL of methyl 6-bromohexanoate, 0.125 g (9.04×10^{-4}mol) of K_2CO_3, and 0.0003 g (1.2×10^{-5}mol) of NaH, 0.0855 g of (1.52×10^{-3}mol) KOH. The components were stirred for 5 min and the reaction proceeded under refluxing for 9.5 h.

The mixture obtained from the previous reaction was added into crushed ice. After, washing of the product was performed with chloroform, and 3 × with distilled water and once with solution of NaCl. Water was removed using Na_2SO_4. Rotary evaporator was used to remove the solvent. The product was separated by column chromatography using chloroform:methanol (32:1 → 1:1) and silica gel 60 as a stationary phase.

^{1}H NMR: δ: 1.34(m, 2H); 1.64(m, 2H); 2.0(m, 2H); 2.3(t, J=11 Hz, 2H); 4.41(t, J=10.5 Hz, 2H); 7.27(m, 6H); 7.47(m, 4H), ppm;

^{13}C NMR: δ: 179.3, 131.3, 130.2, 129.7, 128.7, 128.4, 55, 33.9, 29.6, 26.2, 24.3, ppm.

Melting point: 92-98 °C

R_f= 0.25 (CH:Cl_3MeOH, 32:1, v:v)

3.8 Synthesis methyl 4-((4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoate

Removal of water was ensured by oven dried glass, was performed. 3 mL of freshly distillated THF was added to the flask, followed by 0.01904 g (5.02×10^3 mol) of NaH. 0.12 g (5.3×10^{-4}mol) of 4-(bromomethyl) phenyl acetic acid was in solution added to the round bottom flask. The components were stirred for 5 min and after the reaction preceded at 70 °C for 3 h monitored by GCMS. Purification of the product was performed similarly as described for synthesis of methyl 6-(4,5-diphenyl-2H-1,2,3-triazol-2-yl)hexanoate.

^{1}H NMR: δ: 3.8 (s, 3H); 5.4 (s,2H); 6.9 (d, J=10 Hz, 2H); 7.03 (d, J=7 Hz, 2H); 7.1 (m, 3H); 7.31 (m, 2H); 7.4 (m, 1H); 7.5 (d, J=6.5 Hz, 2H); 7.8 (d, J=8 Hz,2H); 9.45(s, 0.5H), ppm.

^{13}C NMR: δ: 166.6, 144.7, 140.4, 134.1, 130.1, 129.4, 128.6, 127.9, 127.7, 127.5, 126.8, 52.3, 51.8, ppm.

R_f= 0.53 (CH:Cl_3MeOH, 32:1, v:v)

4 DISCUSSION

The main purpose of the research was to synthetize supramolecular components based on the adamantane and 1,2,3-triazole. The synthesis of such compounds was achieved through a series of chemical reactions including 1,3-dipolar cycloadition, radical reaction, esterification, and nucleophilic substitution . Two main final products were formed, namely methyl 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoate and methyl 4-((4,5-diphenyl-1*H*-1,2,3-triazol-2-yl)methyl)benzoate. The synthesis of the former one requires the formation of 4,5-diphenyl-2*H*-1,2,3-triazole and methyl 6-bromohexanoate, while the latter requires the previous synthesis of 4,5-diphenyl-2*H*-1,2,3-triazole and methyl 4-(bromomethyl)benzoate.

To synthetize 4,5-diphenyl-2*H*-1,2,3-triazole, a 1,3-dipolar cycloadition reaction was performed by using sodium azide and diphenylacetylene as chemical reagents Figure 19. It was seen that increasing reaction temperature favored the yield of the product. GCMS, ^{1}H NMR, ESI-MS and HPLC were used to identify the desired product. The purity of white colored powder of 4,5-diphenyl-2*H*-1,2,3-triazole was 96 % (w/w) according to GCMS.

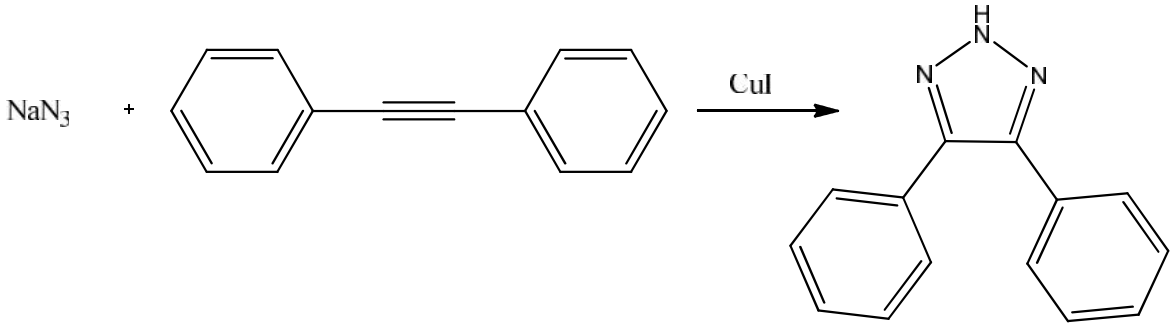


Figure 19. Synthesis of 4,5-diphenyl-2*H*-1,2,3-triazole

After, methyl 6-bromohexanoate was synthetize as described in Figure 20, where 6-bromohexanoic acid and methanol were reacted by the Fisher esterification. GCMS was used to ensure the formation of the ester. The product was recovered in the liquid phase and had a yellow appearance.

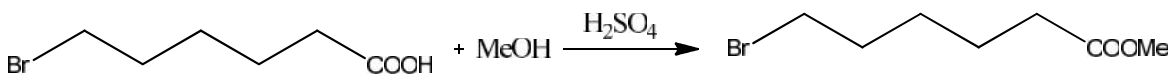


Figure 20. Synthesis of methyl 6-bromohexanoate

As described in Figure 21, the previous formed compounds was allowed to react by nucleophilic substitution to give methyl 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoic acid. ^{1}H NMR was used to identify the product. The product was recovered with a white coloration. Unexpectedly, hydrolisation of methyl ester occurred as 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoic acid. The NMR results showed the symmetry of the molecule.

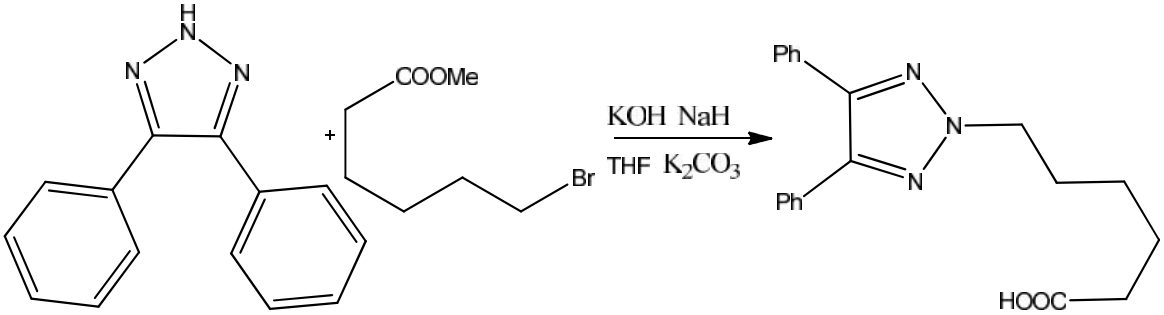


Figure 21. Synthesis of methyl 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoic acid

The synthesis of methyl 4-(bromomethyl)benzoate required an esterification and a radical reaction. In the first step, *p*-tolyl acetic acid was converted into methyl-4-methylphenylacetate by reaction with MeOH in acid medium obtaining a yield of 91 %. GCMS was used to identify the formation of the ester. Figure 22 shows the reaction. The product presented a characterized yellow coloration.

Figure 22. Synthesis methyl-4-methylphenylacetate

The radical reaction required the presence of methyl-4-methylphenylacetate. The reaction was accomplished by a two steps mechanism including initiation and propagation. The presence of incandescent light is necessary for the beginning of the reaction. As can be seen in figure 23, the final product was 4-(bromomethyl)phenyl acetic acid, which was confirmed by GCMS and ^{1}H NMR. The analysis by ^{1}H NMR was helpful to identify the position of the brome atom in which several substituted brome compounds were recognized. 4-(bromomethyl)phenyl acetic acid was identified and isolated to proceed to the formation of a white colored 2-(4-(2-(methylperoxy)ethyl)phenyl)-4,5-diphenyl-2*H*-1,2,3-triazole. This compound was not totally purified as it will be raw material for further research.

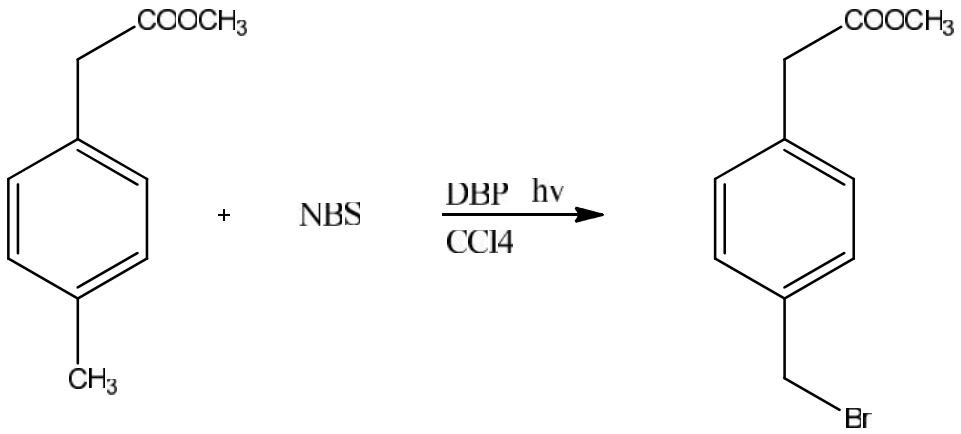


Figure 23. Synthesis of 4-(bromomethyl)phenyl acetic acid

The formation of methyl 4-((4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoate was accomplished by the reaction of 4,5-diphenyl-2*H*-1,2,3-triazole with 4-(bromomethyl)phenyl acetic acid as shown in Figure 24. The reaction proceeded in similar way as described for the formation of methyl 6-(4,5-diphenyl-2*H*-1,2,3-triazol-2-yl)hexanoate but without KOH and K_2CO_3. ^{1}H NMR was used to identify the desired compound whose coloration was similar to a gray color. A nonsymmetrical molecule was detected by the NMR.

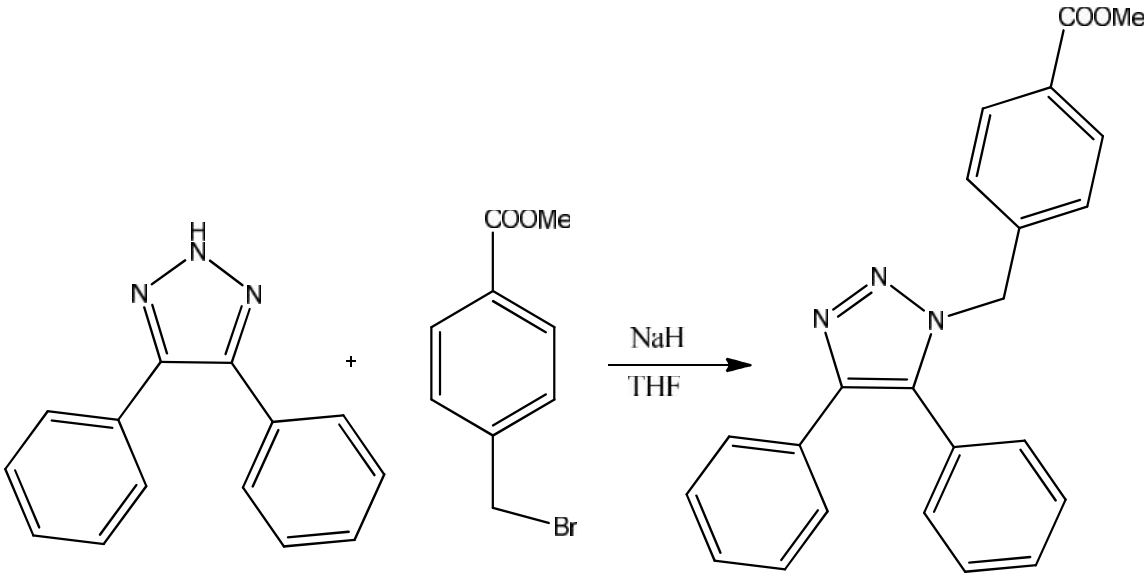


Figure 24. Synthesis of methyl 4-((4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoate

CONCLUSION

This research was focused on the proposal of a model reaction for the future synthesis of supramolecular components based on the adamantane and 1,2,3-triazole. Successful synthesis of 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) was achieved by means of 1,3-dipolar cycloadition, radical reaction, esterification and nucleophilic substitution.

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LIST OF ABBREVIATIONS

DMSO	Dimethyl sulfoxide,
CuI	Copper (I) Iodide
MeOH	Methanol,
$CaCl_2$	Calcium chloride
NaH	Sodium hydrogen
THF	Tetrahydrofurane
KOH	Potassium hydroxide
K_2CO_2	Potassium carbonate
NBS	*N*-bromosuccinimide
DBP	dibenzoyl peroxide
$[Cp^*RuCl]_4$	Pentamethylcyclopentadienyl ruthenium(II) chloride tetramer
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
GCMS	Gas chromatography–mass spectrometry
IR	Infrared
PCR	Polymerase chain reaction
^{13}C NMR	Carbon-13 NMR
^{1}H NMR	Hydrogen-1 NMR

LIST OF FIGURES

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