SYNTHESIS AND CHARACTERIZATION OF ACETYLENIC DIOLS DERIVED FROM 1-ETHYNYLCYCLOHEXANOL AND CARBONYL COMPOUNDS

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1-ethynylcyclohexanol, aliphatic, cyclic and aromatic ketones, catalytic system, acetylene diols, product yield, solvents.

ANNOTATSIYA:

For the first time, nucleophilic coupling reactions of 1-ethynylcyclohexanol with some ketones - cyclohexanone, acetophenone, para-chloroacetophenone, adamantanone, methylhexylketone and ethyl-n-butyl ketones were studied using the Bu4NOH/DMSO/H2O catalytic system. New acetylene diols – 1-(2-(1-hydroxycyclohexyl)ethynyl)cyclohexanol (1), 1-(3-hydroxy-3-phenylbut-1-ynyl)cyclohexanol (2), 1-(3-(4-chlorophenyl)-3-hydroxybut-1-ynyl) cyclo-hexanol(3), 1-(2-(1-hydroxyadamantanyl)ethynyl)cyclohexanol (4), 1-(3-hydroxy-3-methyldec-1-ynyl) cyclohexanol(5) and 1-(3-ethyl-3-hydroxyhept-1-ynyl) cyclohexanol (6) were synthesized in the process. The effects of the catalyst for the synthesis of acetylene diols, the nature of the solvent, the mole ratio of the starting materials, the temperature, and the duration of the reaction were systematically analyzed. The composition, structure and purity of the synthesized acetylene diols were determined by modern physical and chemical research methods.

Introduction

Today, the development of drug preparations to combat cancer remains one of the most pressing issues in many scientific schools worldwide. Notably, in the early 20th century,

scientists from the National Cancer Institute of the United States first determined that compounds containing a triple bond, specifically acetylene diols and their derivatives, exist in plants, fungi, microorganisms, and marine invertebrates, albeit in very small quantities [1, 2].

Significant interest was sparked among scientists globally after Professor Valery M. Dembitsky and his research school identified anticancer properties against tumor cells in over 300 acetylene diols and lipids found in plants [3].

J.G. Ferreira and colleagues synthesized acetylene diols with a yield of 62-92% via the reaction of dilithium alkynolate, formed from terminal acetylene with n-butyllithium catalyst in THF solvent at -78 °C, with ketones in the presence of ammonium chloride. Furthermore, acetylene diol enantiomers (up to 99% yield) were obtained from acetylene dioxydiacetylene in the presence of potassium carbonate and methanol solvent over 2 hours at room temperature via an enzymatic method involving lipase B. Tests confirmed that the synthesized acetylene diols possess anticancer properties [4].

J.L. Princival and J.G. Ferreira achieved the highest yield (90%) for an alternative synthesis of acetylene diols by reacting acetylene bis-lithium salt with paraformaldehyde using 0.5 mmol of $CeCl_3$ as a Lewis acid catalyst at -40 °C for 4 hours [5].

Spanish scientist Abdeslam Abou and his team synthesized a 1:1 mixture of acetylene diol diastereomers with 36-95% yield via the alkynylation of vicinal dihalogen derivatives of alkynes with ketones or aldehydes using lithium naphthalenide. The process was conducted in THF at -78 °C for 3 hours. Using a catalytic system of DTBB (1,4-di-tert-butylbenzene) and lithium metal instead of lithium naphthalenide yielded acetylene diols with 39-59% efficiency [6].

In organic synthesis, certain acetylene alcohols, widely used as intermediates in nucleophilic addition reactions forming C-C bonds between aldehydes/ketones and alkynes via various catalytic systems, have been synthesized [7-11]. Specifically, acetylene alcohols and diols have also been obtained based on the initial stoichiometric metal-catalytic addition of alkynes in the presence of organometallics (lithium organic compounds, Grignard reagent), followed by catalytic activation of the alkyne derivatives for addition to the carbonyl group [12-14]. Zinc organic catalysts demonstrated high yields in alkynylation reactions of aldehydes with alkynes. For the synthesis of acetylene alcohols, a number of metal complex catalysts (Ag [15], Rh [16], In [17], Cr [18], Ti [19], Cu [20], Ru [21], and Pd [22]) have also been used successfully. However, these methods have recognized drawbacks, including the toxicity and high cost of some catalysts in this category, as well as challenges such as removing metal residues during the synthesis of pharmacological preparations.

Furthermore, a phase-transfer method using fluorobenzene as the organic phase and a $Bu_4NBr/NaOH/H_2O$ catalytic system was employed for the ethynylation of aldehydes and

ketones, but the reaction of aromatic aldehydes and ketones with phenylacetylene yielded low product outputs (30-35%) [23]. Quaternary ammonium organic salts such as Bu_4NF, Bu_4NCl, Bu_4NBr, Bu_4NI, Me_4NBr, and HTAB were analyzed for the alkynylation process of aryl ketones with arylacetylenes. The best yield for this alkynylation was achieved using THF solvent, 10 mmol KOH, and 0.1 mmol Bu_4NCl over 3 days at room temperature [24].

Research Method

Synthesis of 1-(2-(1-Hydroxycyclohexyl)ethynyl)cyclohexanol in a $Bu_4NOH/DMSO/H_2O$ Catalytic System:

The reaction was carried out in a specially prepared double-walled 5000 ml reactor equipped with a mechanical stirrer (SPXFLOW Lightnin LB2, 20/150/2500 rpm), a dropping funnel (IsoLab TS29/32, 200 ml capacity), a reflux condenser (Dimrota TS29/32, 160 mm), and a ground-glass thermometer (Thermometer LLG-General -10/+250 °C). First, 259 g (1 mol) of Bu_4NOH (40% aqueous solution) and 300 ml of DMSO were stirred at 10 °C for 60 minutes to form a suspension. To the resulting catalytic system, 124 g (1 mol) of 1-ethynylcyclohexanol was added, and hydroquinone was introduced to prevent polymerization of the acetylene alcohol and the forming acetylene diols. Subsequently, 1 mol (98 g) of cyclohexanone was added dropwise over 60 minutes with continuous stirring, after which the mixture was left to stand for 12 hours. The reaction mixture was diluted with cold water (1:1) and extracted three times with diethyl ether (3×50 ml).

The organic phase was washed with water (3×100 ml) and dried over Na_2SO_4 for 2 hours. The product was filtered, solvents were evaporated using a vacuum rotary evaporator (Hei–VAP Core HL/G3, Germany), and then passed through a silica gel 60 chromatography column using a hexane/ethyl acetate eluent mixture. Fractions were analyzed by thin-layer chromatography (“Merck 60 F254” plates) to determine Rf values. This procedure yielded 192 g of 1-(2-(1-hydroxycyclohexyl)ethynyl)cyclohexanol (86%), 12.4 g of intermediate product (5%), 6.8 g of starting materials (3%), and 14.2 g of by-products (6%).

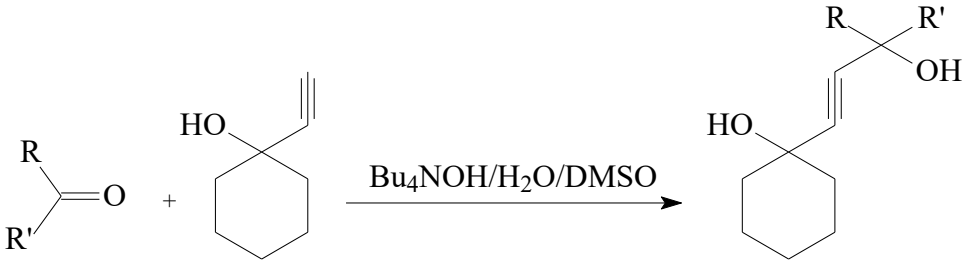
Results and Discussion

Using this method based on the $Bu_4NOH/H_2O/DMSO$ catalytic system prepared from tetra-n-butylammonium hydroxide and DMSO, the following acetylene diols were synthesized via reactions of 1-ethynylcyclohexanol with various aliphatic, cyclic, and aromatic ketones—cyclohexanone, acetophenone, para-chloroacetophenone, adamantanone, methyl hexyl ketone, and ethyl n-butyl ketone—in a basic medium:

1. 1-(2-(1-Hydroxycyclohexyl)ethynyl)cyclohexanol (1)
2. 1-(3-Hydroxy-3-phenylbut-1-ynyl)cyclohexanol (2)
3. 1-(3-(4-Chlorophenyl)-3-hydroxybut-1-ynyl)cyclohexanol (3)
4. 1-(2-(1-Hydroxyadamantyl)ethynyl)cyclohexanol (4)
5. 1-(3-Hydroxy-3-methyldec-1-ynyl)cyclohexanol (5)

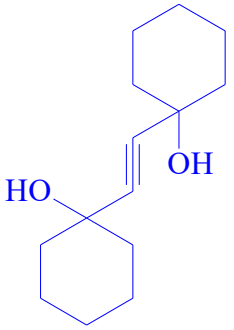
6. 1-(3-Ethyl-3-hydroxyhept-1-ynyl)cyclohexanol (6)

The proposed reaction scheme is as follows [25].



1–6

where : RR′= - $_c$Hex (1); R= -Me, R′= -Ph (2); R= -Me, R′= -Ph$_p$Cl (3); RR′ = -Ad (4); R= -Me, R′= -Ht (5); R= -Et, R′= -Bu (6)



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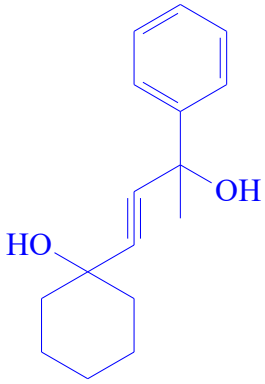

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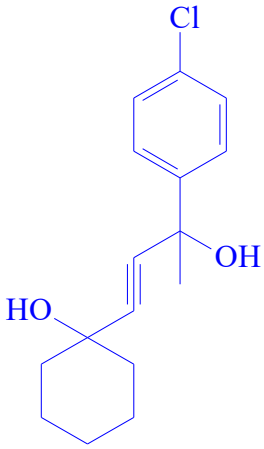

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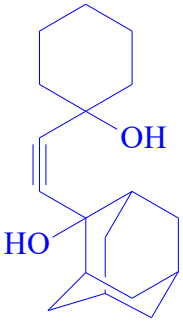

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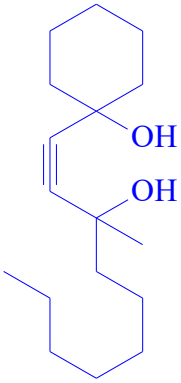

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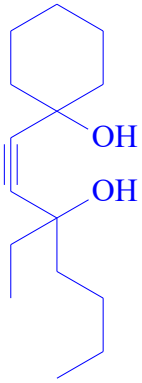

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The effects of temperature, reaction duration, solvent, catalyst nature, and molar ratios of starting materials on the yield of acetylene diols were systematically analyzed. Initially, the synthesis of acetylene diols was conducted in aprotic solvents—dimethylformamide (DMFA), dimethyl sulfoxide (DMSO), acetone (ASE), and tetrahydrofuran (THF)—and

their impact on product yield efficiency was studied. The obtained results are presented in Fig. 1.

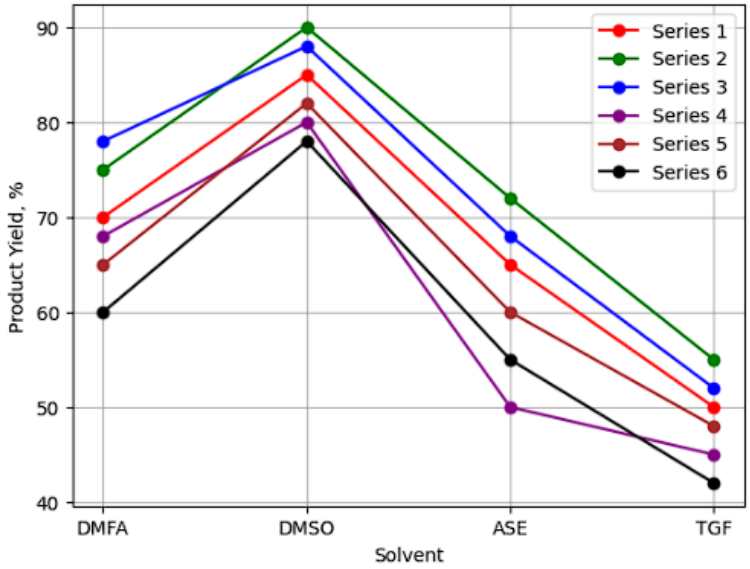

Fig. 1. Effect of Solvent Nature on the Yield of Acetylene Diols
(Catalyst: Bu_4NOH).

Although the used aprotic solvents exhibited favorable conditions for SN_2 reactions, analysis of the results determined that the product yield was relatively higher in DMSO. This process is explained as follows:

- DMFA and DMSO, being bipolar aprotic solvents, facilitate nucleophilic substitution reactions. However, DMFA's manifestation of two different spatial configurations leads to a decrease in the number of collisions with ions. Furthermore, the lower solubility of acetylene derivatives in DMFA compared to DMSO causes a reduction in the yield of acetylene diols.
- Compared to DMFA, THF, and ASE (acetone), DMSO has a higher dielectric constant ($\varepsilon = 40$). This leads to a higher degree of dissociation of ion pairs, poor stabilization of anions, and high stability of cations. DMSO's ability to dissolve alkynes very well, along with its partial catalytic properties in SN_2 reaction mechanisms, resulted in an increased product yield. Consequently, acetylene diols 1–6 were synthesized with yields of 86%, 92%, 89%, 80%, 85%, and 82%, respectively.
- The existence of keto-enol tautomerism in acetone, similar to most ketones, its low number of spatial collisions of ions in solution, and its small dipole moment lead to a decrease in product yield in the reaction.
- THF's low dielectric constant ($\varepsilon = 7.6$) and the insufficient number of spatial collisions between alkyne ions and ketones result in a decreased yield.

The effect of reaction duration on the yield of acetylene diols was analyzed in the range of 60–180 minutes (presented in Fig. 2).

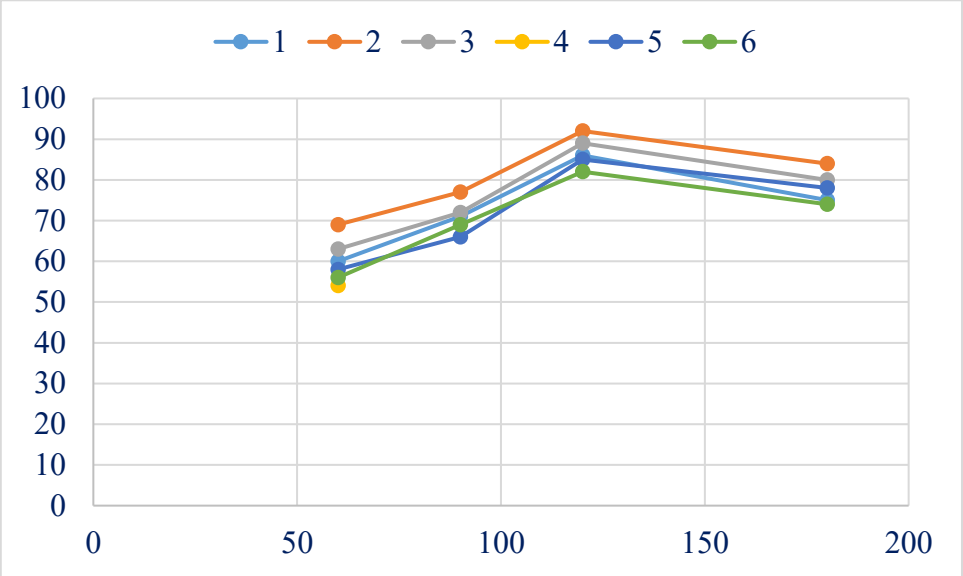

Fig. 2. Effect of Reaction Duration on the Yield of Acetylene Diols
(Catalyst: Bu_4NOH, Solvent: DMSO, Temperature: 10 °C).

At a temperature of 10 °C in a medium of tetrabutylammonium hydroxide and DMSO solvent, when the reaction was carried out for 60 and 90 minutes, thin-layer chromatography analysis revealed that the starting reagent (1-ethynylcyclohexanol) and substrate (ketone) did not fully react with each other. Consequently, an efficient product yield was not achieved. The results of physicochemical analysis indicated that the process proceeded more completely over 120 minutes. This is because the starting materials fully dissolved in DMSO, exhibited a high degree of dissociation, and the number of collisions at the active reaction centers of acetylene alcohols with ketones was high. This led to an increase in the yield of acetylene diols, specifically: **1** from 71% to 86%, **2** from 77% to 92%, **3** from 73% to 89%, **4** from 64% to 80%, **5** from 66% to 85%, and **6** from 69% to 82%.

For the first time, acetylene diols were synthesized via an enantioselective nucleophilic addition reaction of ketones with different natures to 1-ethynylcyclohexanol using a highly basic catalytic system—$Bu_4NOH/DMSO/H_2O$.

The influence of a number of factors on the product yield and the course of the reaction was systematically investigated, and based on the obtained results, the most optimal conditions for the processes were determined. Accordingly, for the nucleophilic addition reaction of selected ketones with 1-ethynylcyclohexanol, the highest yield of acetylene diols was achieved under the following conditions: temperature 20 °C, molar ratio of 1-ethynylcyclohexanol:ketone:catalyst = 1:1:1, solvent DMSO, and reaction duration of 120 minutes.

Analysis of the selected solvents for acetylene diol synthesis—DMFA, DMSO, acetone, and THF—showed that the highest yield was obtained in DMSO.

The structure, composition, properties, and purity of the synthesized acetylene diols were studied using modern physico-chemical research methods.

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