

Short Note

# 8,13-Dimethylcosa-9,11-diyne-8,13-diol

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**Abstract:** The protocol, 3-methyldec-1-yn-3-ol (**1a**) was chosen to perform the dimerization process. The optimal conditions for synthesis of 8,13-dimethylcosa-9,11-diyne-8,13 (**2a**) with high efficiency when using copper-catalyzed, N,N,N',N'-tetramethylethylenediamine as a ligand and CCl<sub>4</sub> and methanol solvents in atmospheric pressure were determined. The structure of the obtained compound was proved by IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectroscopy.

**Keywords:** terminal acetylene alcohol; diacetylene diol; dimerization; oxidative homocoupling reaction; copper (I) chloride

## 1. Introduction

Recently, the attention of chemists, technologists and pharmacologists has focused on the elaboration and implementation of new drugs with effective pharmacological effects [1]. In this regard, diacetylene diols and their derivatives were attributed to biologically active organic compounds with pharmacological properties, such as anti-cancer [2,3], anti-bacterial [4], anti-HIV [5], anti-fungal [6] and anti-inflammatory [7–10]. Moreover, when the pharmacology of mono and diacetylene diol derivatives, including panaxynol, panoxydol, panaxydolcglorohydrin, 1,8-heptadecadiene-4,6-diyne-3,10-diol, panaxytriol and dihydropanaxacol, was studied, some of them were used for the treatment of alopecia (a disease with hair loss) due to their hair growth properties [11]. It was found that heptadeca-8,16-diene-4,6-diyne-3,10-diol extracted from the plant *Aralia dumetorum* possesses inhibitory properties against harmful toxins [12].

Glaser first synthesized 1,4-diphenylbuta-1,3-diyne from phenylacetylene through the dimerization reaction in the presence of copper (I) chloride and oxygen [13]. J.S. Yadav and his team synthesized 1,4-diphenyl-1,3-butadiene with 95% yield from phenylacetylene based on oxidative homocoupling–dimerization reactions 1-butyl-3-methylimidazolium hexafluorophosphate (bmim-PF<sub>6</sub>) and 1-butyl-3-methylimidazolium tetrafluoroborate (bmim-BF<sub>4</sub>) in the presence of copper (I) chloride (0.2 mol%), TMEDA (0.2 mol%) in oxygen atmosphere [14]. Yun Lia, Reza Fathi and others succeeded in synthesizing symmetrical bis-benzo[b]furan-linked 1,3-diyne through homocoupling of three bonds using the new catalytic system AgOTs–CuCl<sub>2</sub>–TMEDA. It was also observed for the first time that the reaction rate of the oxidative acetylenic homocoupling process based on activated Ag (I) cation with triple bond and Cu (II) cation was very high, the product was obtained with a yield of 70–90% and the reaction mechanism was proposed [15]. Several derivatives of 1,3-diyne, such as 1,4-dip-tolylbuta-1,3-diyne, 1,4-diphenylbuta-1,3-diyne, 1,4-bis(4-trifluoromethyl)phenyl)buta-1,3-diyne, 1,4-bis(4-(trifluoromethyl) phenyl)buta-1,3-diyne, 1,4-bis(4-methoxyphenyl)buta-1,3-diyne, 1-(cyclohex-3-enyl)-4-cyclohexenylbuta-1,3-diyne, 1,1'-buta-1,3-diyne-1,4-diyldicyclohexanol, hexadeca-7,9-diyne and dodeca-5,7-diyne dinitrile (produced with 78–87% yields) were synthesized when the oxidative homocoupling reaction was carried out in the presence of catalyst Pd(OAc)<sub>2</sub> or PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>



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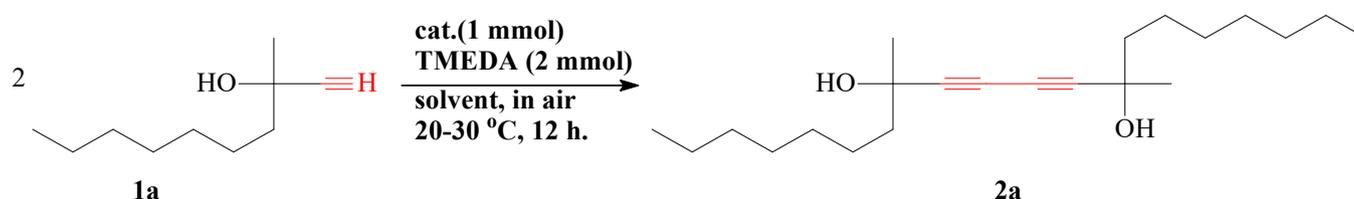


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and 1-(2-pyridylethynyl)-2-(2-thienylethynyl)benzene as a ligand and solvent  $\text{NEt}_3$  [16]. Diacetylene diols such as octa-3,5-diyne-1,8-diol and 2,7-dimethyl-3,5-octadiyne-2,7-diol were efficiently formed when the homocoupling reaction was carried out from terminal acetylene alcohols using the  $\text{Cu}(\text{OAc})_2/\text{MgAl-LDH}/\text{TMEDA}/\text{CH}_3\text{CN}$  catalytic system [17]. Piperidine,  $\text{Bu}_3\text{N}$ ,  $\text{Bu}_2\text{NH}$  and several solvents (toluene, 1,4-dioxane,  $\text{Cl}_2\text{CHCHCl}_2$ , DMSO and DMF) were studied as various additives to increase the catalytic activity to obtain with high yield in the dimerization reaction of heptin-1 in the presence of the  $\text{CuCl}$  catalyst. Tetradeca-6,8-diyne was synthesized with high yield when the process was carried out at  $60^\circ\text{C}$  in a 2:10 mol ratio of toluene solvent and  $\text{CuCl}$ :piperidine, respectively [18].

## 2. Results and Discussion

In this work, the dimerization reaction of terminal acetylene alcohol 3-methyldec-1-yn-3-ol (**1a**) was carried out for the first time. Alternative conditions for the synthesis of 8,13-dimethylcosa-9,11-diyne-8,13-diol (**2a**) containing two triple bonds and two hydroxy (-OH) groups were analyzed. Synthesis of **2a** was carried out through the dimerization reaction of terminal acetylene alcohol as **1a** in the presence of  $\text{CuCl}/\text{TMEDA}/\text{CCl}_4/\text{MeOH}$  catalytic system. The reaction scheme is given below (Scheme 1).



Scheme 1. Synthesis of **2a**.

The dimerization process was studied at of  $20\text{--}30^\circ\text{C}$  with  $\text{CuCl}$ ,  $\text{CuJ}$  and  $\text{CuBr}$  (1.0 mmol) catalysts in TMEDA (*N,N,N',N'*-tetramethylethylenediamine) (2.0 mmol),  $\text{CCl}_4$  in various solvents— $\text{MeCN}$ , THF,  $\text{CH}_2\text{OHCH}_2\text{OH}$ , *iPrOH*, ethanol and methanol (Table 1).

Table 1. Optimization of catalyst and solvent effect.

Entry	Catalyst	Solvent	Additive	Time, h.	Yield, % <sup>a</sup>
1	$\text{CuCl}$	$\text{MeCN}/\text{CCl}_4$	TMEDA	8	trace <sup>b</sup>
2	$\text{CuCl}$	$\text{THF}/\text{CCl}_4$	TMEDA	10	42
3	$\text{CuCl}$	$\text{CH}_2\text{OHCH}_2\text{OH}/\text{CCl}_4$	TMEDA	10	27 <sup>b</sup>
4	$\text{CuCl}$	<i>iPrOH</i> / $\text{CCl}_4$	TMEDA	12	65
5	$\text{CuCl}$	$\text{EtOH}/\text{CCl}_4$	TMEDA	12	70
6	$\text{CuCl}$	$\text{MeOH}/\text{CCl}_4$	TMEDA	12	82
7	$\text{CuCl}$	$\text{MeOH}/\text{CCl}_4$		12	trace <sup>b</sup>
8	$\text{CuJ}$	$\text{MeOH}/\text{CCl}_4$	TMEDA	12	64
9	$\text{CuBr}$	$\text{MeOH}/\text{CCl}_4$	TMEDA	12	56

<sup>a</sup> determined by  $^1\text{H}$  and  $^{13}\text{C}$ -NMR; <sup>b</sup> isolated yield.

When the process was carried out for 8 h in the catalytic system  $\text{CuCl}/\text{TMEDA}/\text{MeCN}/\text{CCl}_4$ , a very small amount of the product was formed on entry. **2a** was obtained with low yield of 42 and 27%, respectively, when the process was carried out in THF or ethylene glycol with  $\text{CCl}_4$  for 10 h, and this increase in the time did not affect the yield (2–3 entries). The effects of  $\text{CCl}_4$  solvents with *iPrOH* or  $\text{EtOH}$  were studied; **2a** gave moderate yields (4–5 entries). In  $\text{MeOH}/\text{CCl}_4$  for 12 h, **2a** gave the best yield of 82% (six entries) compared to the others. However, in  $\text{MeOH}/\text{CCl}_4$  without addition of this catalytic system, a very small amount of **2a** was obtained (seven entries). Additionally, when  $\text{CuJ}$  or  $\text{CuBr}$  (1 mmol) were used instead of  $\text{CuCl}$ , a decrease in the yield of **2a** was observed (8–9 entries). Based on the research, it was concluded that  $\text{CuCl}$  has high catalytic activity compared to  $\text{CuJ}$  and  $\text{CuBr}$  and based on the oxidative homocoupling reaction of **1a**, the most alternative conditions

for the synthesis of **2a** were determined to be the process: the CuCl/TMEDA/CCl<sub>4</sub>/MeOH catalytic system and time 12 h.

The structure of **2a** obtained by the dimerization reaction of acetylene alcohols was confirmed by spectroscopic methods. (<sup>1</sup>H, <sup>13</sup>C-NMR and IR; see also Supplementary Materials). In particular, the chemical shift region of 2.41 ppm in the <sup>1</sup>H-NMR spectrum of the starting product **1a** (Figure S1), the loss of this singlet was observed in the <sup>1</sup>H-NMR spectrum of **2a** (Figure S3).

### 3. Materials and Methods

#### 3.1. General

The major chemicals, such as copper (I) chloride, copper (I) iodide, copper (I) bromide, TMEDA (N,N,N',N'-tetramethylethylenediamine), tetrachloromethane, tetrahydrofuran, acetonitrile, ethylene glycol, ethanol and methanol, were purchased from Qingdao Sigma Chemical Co., Ltd. (Qingdao, China). First, **1a** [19] was synthesized according to the literature procedures and its structure was proved by the <sup>1</sup>H and <sup>13</sup>C-NMR spectra. All reagents were used at reagent grade or used after distillation. Additionally, solvents were dried by standard methods before use. All reactions were carried out by stirring in the magnetic stirrer under atmospheric air condition, and the reaction progress was the identity of the synthesized compounds controlled by TLC analysis, which was performed on Merck Silica gel 60 GF<sub>254</sub> plates. Column chromatography was performed on silica gel and visualization in UV light. IR spectra of the synthesized compounds were recorded on The Thermo Scientific Nicolet iS50 FT-IR spectrometer, (Raman module, Waltham, MA, USA); <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded on Bruker Avance (400.1 and 100.6 MHz, respectively) spectrometer at 20–25 °C in CDCl<sub>3</sub>, solution using the solvent line as an internal reference. Multiplicities are marked as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet.

#### 3.2. Synthesis of **2a**

A one-necked 50 mL round-bottom flask (or 12 mL vial) was charged with **1a** (1.0 mmol, 0.168 g), TMEDA (2 mmol, 0.255 g), CuCl (1.0 mmol) in MeOH (2 mL) in atmospheric air conditions. The reaction mixture was kept at 20–30 °C under stirring for 30 min using an ultrasonic irradiation bath. CCl<sub>4</sub> 0.2 mL was added slowly and mixed for 12 h on the magnetic stirrer. Volatiles were evaporated in vacuo, and the residue was purified by column chromatography using appropriate mixtures of hexane and CH<sub>2</sub>Cl<sub>2</sub> (3:1 followed by 1:1 and 0:1) as eluents. Slightly brown oil, yield 0.274 g (82%). <sup>1</sup>H-NMR (400.1 MHz, CDCl<sub>3</sub>): 2.02 (s, 2H, 2OH), 1.71–1.59 (m, 4H, 2CH<sub>2</sub>), 1.52–1.40 (m, 10H, 2CH<sub>2</sub>, 2CH<sub>3</sub>), 1.34–1.21 (m, 16H, 8CH<sub>2</sub>), 0.87 (t, 6H, 2CH<sub>3</sub>, *J* = 6.9 Hz); <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 83.2, 68.7, 67.4, 43.5, 31.8, 29.6, 29.5, 29.2, 24.6, 22.6, 14.1. IR: 3367 cm<sup>-1</sup> (–OH), 2954–2855 cm<sup>-1</sup> (–CH<sub>2</sub>), 2216 cm<sup>-1</sup> and 2046 cm<sup>-1</sup> (–C≡C–), 1458–1370 cm<sup>-1</sup> (–CH<sub>2</sub>), 1307–1253 cm<sup>-1</sup> (–CH<sub>2</sub>), 1220–1098 cm<sup>-1</sup> (C–O–H), 1016–733 cm<sup>-1</sup> (–CH<sub>2</sub>). HRMS (ESI-TOF): *m/z* [M – H]<sup>+</sup> Calcd for C<sub>22</sub>H<sub>37</sub>O<sup>+</sup>: 317.2839; found: 317.2848.

### 4. Conclusions

For the first time, the dimerization reaction of acetylene alcohol **1a** was carried out in the CuCl/TMEDA/CCl<sub>4</sub>/MeOH catalytic system. 8,13-Dimethylcosa-9,11-diene-8,13-diol was synthesized with 82% yield. Alternative conditions for the dimerization reaction were determined by studying the effects of copper (I) halides, N,N,N',N'-tetramethylethylenediamine and solvents.

**Supplementary Materials:** The following supporting information for the characterization of **1a** and **2a** can be downloaded online: Synthesis and reaction scheme of **1a** and **2a** (Scheme S1: Synthesis of 3-methyldec-1-yn-3-ol). Figure S1: <sup>1</sup>H-NMR spectrum of **1a** (400 MHz, CDCl<sub>3</sub>); Figure S2: <sup>13</sup>C-NMR spectrum of **1a** (101 MHz, CDCl<sub>3</sub>); Figure S3: <sup>1</sup>H-NMR spectrum of **2a** (400.1 MHz, CDCl<sub>3</sub>); Figure S4: <sup>13</sup>C-NMR spectrum of **2a** (100.6 MHz, CDCl<sub>3</sub>); Figure S5: IR spectrum of **2a** (The Thermo Scientific Nicolet iS50 FT-IR spectrometer, Raman module, Waltham, MA, USA).

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