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Synthesis of bis (1,4-disubstituted-1,2,3-triazoles) starting from diethyl galactarate

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Abstract: This communication reports the synthesis of a series of bis (1,4-disubstituted-1,2,3-triazoles) starting from the known (2,3,4,5) bis acetonide protected diethyl galactarate (**1**). Reduction of **1** with LiAlH$_4$ led to dioxolane **2** (90%), which upon treatment with CBr$_4$ gave the corresponding dibromide **3** (80%). The reaction of **3** with NaN$_3$ in DMF afforded the key diazide **4** (95%). From diazide **4** were obtained the bis (1,4-disubstituted-1,2,3 triazoles) **5-8** *via* click reactions with alkyl substituted acetylenes including triphenyltinacetylene. Physical characteristics of the new compounds including selected values^{1}H, ^{13}C, and ^{119}Sn NMR data are given.

Keywords: Bis (1,4-disubstituted-1,2,3-triazoles); triphenyltin substituents; galactaric framework; physical properties

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1. Introduction

As shown in a large number of publications, 1,2,3-triazoles have found wide application in diverse areas of agriculture and medicine. In this sence, the vast existing literature demonstrate the antifungal, anticonvulsant, antiviral, antibacterial, antimalarial and antidiabetic properties of these compounds [1]. On the other hand, natural products like galactose, glucose, fructose, and manose, are useful and cheap raw materials available in industrial scale. This makes these renewable multifunctional compounds useful for the synthesis of organic ligands, catalysts, and also chiral molecules of industrial interest. Click chemistry provides a valuable tool for the preparation of 1,2,3-triazoles *via* cycloaddition reactions between alkynes and azides [2].

In this communication we report the synthesis of some new bis (1,4-disubstituted-1,2,3 triazoles) starting from the commercially available diethyl galactarate. Also some physical properties of these compounds are reported.

2. Results and discussion

The synthesis of compounds with galactaric framework **2-6**, was carried out according to Scheme 1. The reaction of diethyl galactarate with acetone anh. in the presence of triethylboron etherate led to (2,3,4,5) bis acetonide protected diethyl galactarate (**1**) in 61% yield. The reduction of **1** with LiAlH$_4$ led to ((4S,4'R,5R,5'S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolane)]-5,5'-diyl)dimethanoldiol (**2**) in 90% yield. Compounds **1-3** have already been reported [3]. Diol **2** by reaction with CBr$_4$ and PPh$_3$ in CH$_2$Cl$_2$., gave (4R,4'S,5S,5'R)-bis(bromomethyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (**3**) in

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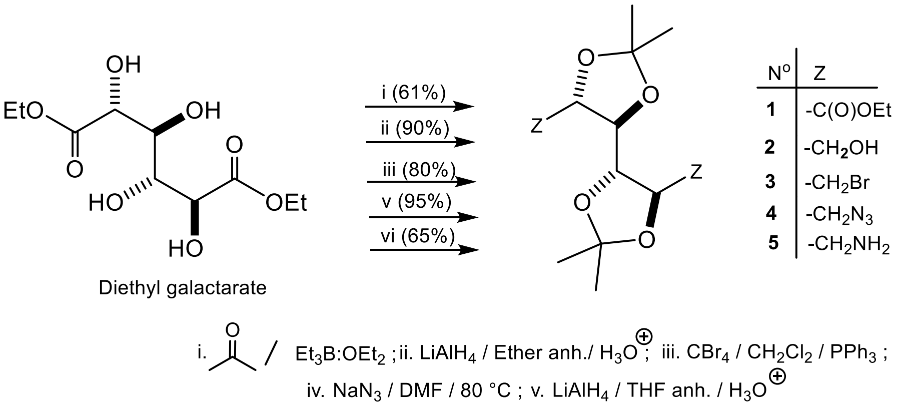
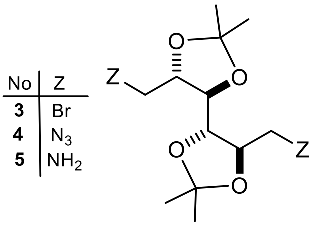
80% yield. Compound **3** is a white solid of mp 120-122 °C. The reaction of dibromide **3** with NaN_3 in DMF at 80 °C, afforded (4S,4'R,5R,5'S)-5,5'-bis(azidomethyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (**4**). Diazide **4**, a white solid compound mp 70-71 °C, was obtained in 95% yield, and was the key compound for the synthesis of the target compounds, i.e., the bis (1,4-disubstituted-1,2,3 triazoles). The reduction of **4** with $LiAlH_4$ led to ((4 ((4S,4'R,5R,5'S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolane)]-5,5'-diyl) dimethanamine (**5**), a white solid mp 64-67 °C, in 65% yield. ^1H NMR characteristics of compounds **3**-**5** are included in Table 1.



Scheme 1. Synthesis of compounds with galactaric framework **1**-**5**

Table 1. ^1H NMR characteristics of compounds **3**-**5**.[a]

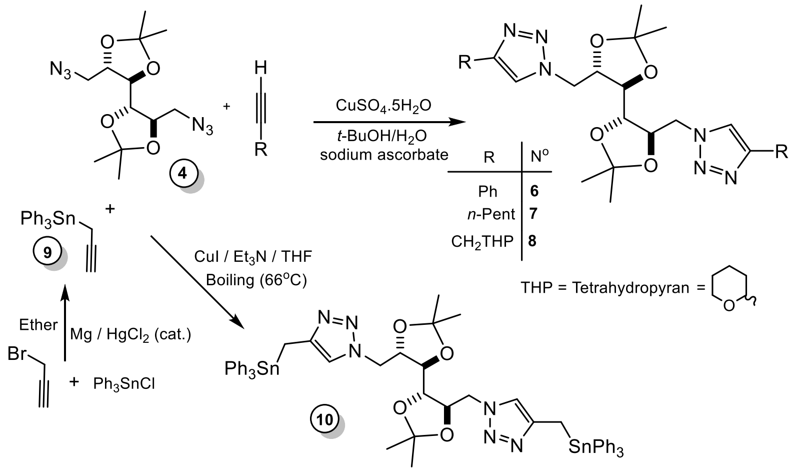


Comp. N°	Chemical shifts (δ, ppm)[a]
3	1.41 (s, 6H); 1.77 (s, 6H); 3.52 (m, 2H); 3.69 (m, 2H); 3.82 (m, 2H)
4	1.31 (s, 6H); 1.38 (s, 6H); 3,22-3.28 (m, 2H); 3.56-3.62 (m, 2H); 3.70-3.73 (m, 2H); 4.03-4.09 (m, 2H)
5	1.29 (s, 6H); 1.32 (s, 6H); 2.15 (s, 4H; NH_2 x 2); 2.76 (m, 2H); 2.90 (m, 2H); 3.57 (m, 2H); 3.90 (m, 2H)

[a] In $CDCl_3$. Chemical shifts with respect to TMS.

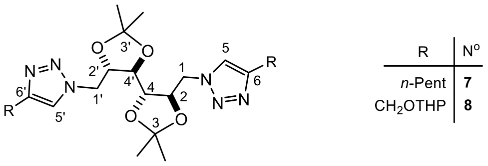
1,3-Dipolar cycloadditions, usually referred to as Huisgen cycloadditions, is one of the most powerful methods for the preparation in excellent yields a wide range of triazoles, including 1,4-disubstituted 1,2,3-triazole [2,4]. In order to obtain molecules with two triazo substituents, we consider it of interest to explore the use of click reactions [4].

In this communication we inform the synthesis of some bis (1,4-disubstituted 1,2,3-triazole) using as starting material diazide **4**. The reactions were carried out by preparing a suspension of **4** (0.48mmol) and the terminal alkyne (0.97 mmol) in a mixture 1:1 of t-butanol / water (2 ml). To the suspension was added sodium ascorbate (0.05 ml of an aqueous 1M solution), and then $CuSO_4.5H_2O$ (0.012g, 0.050 mmol). The reaction with stirring was left overnight at RT. The reaction mixture was cooled down to 0 °C, and then water (0.50 ml) was added. It was observed the formation of a precipitate which was filtered giving the desired products in all cases with almost quatitative yields. In Scheme 2 is shown the synthesis of bis (1,4-disubstituted 1,2,3-triazole) **6**-**8** and **10**. In the case of the synthesis of organotin derivative **10**, using the combination sodium ascorbate/$CuSO_4$ in water no reaction was observed. However, the reacction using CuI and Et_3N in THF and under reflux gave 1,1′-(4R,4′S,5S,5′R)-2,2,2′,2′-tetramethyl-[4,4′-bi(1,3-dioxolane)]-5,5′-diyl)bis(methyle)bis[4-(triphenylstannyl)methyl)-1*H*-1,2,3-triazol] (**10**), which was purified by column chromatgraphy. Compound **6** is not soluble in common NMR solvents and it was identified by HRMS-ESI.



Scheme 2. Synthesis of bis (1,4-disubstituted 1,2,3-triazole) **6**-**8** and **10**

Table 2. ^{13}C-NMR characteristics of compounds **7** and **8**.[a]

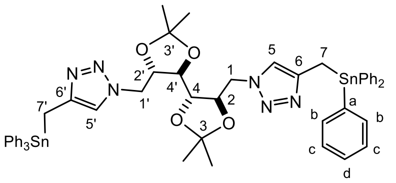


Comp.Nº	Me	C-1 y 1′	C-2 y 2′	C-3 y 3′	C-‘4 y 4′	C-5 y 5′	C-6 y 6′
7[b]	26.99	51.10	79.09	111.01	78.27	122.42	148.45
8[c]	26.93	51.04	78.93	111.00	78.14	121.19	149.53

[a] In $CDCl_3$, chemical shifts, δ, in ppm with respect to $CDCl_3$ central peakl; [b] Other signals: 14.06 ; 22.46 ; 25.69; 29.22; 31.51. [c] 14.93; 58.12; 68.80; 123.63; 128.65.

The triphenylpropargyltin (**9**) needed in order to prepare the bis (1,4-disubstituted 1,2,3-triazole) **10** was obtained from the reaction between propargyl bromide and triphenyltin chloride, carried out in ether in the presence of Mg and catalytic amounts of $HgCl_2$ (Scheme 2). ^{13}C NMR characteristics of compounds **7** and **8** are sumarized in Table 2. In Table 3 are collected the ^{13}C-, ^{1}H and ^{119}Sn NMR characteristics of compound **10**.

Tabla 3. ^{13}C-, ^{1}H and ^{119}Sn NMR characteristics of compound **10**.[a]



Comp. N° **10**	Me	C(1/1′)	C(2/2′)	C(3/3′)	C(4/4′)	C(5/5′)	C(6/6′)	C(7/7′)
^{13}C-NMR [b]	26.86	51.11	78.09	110.80	79.06	121.55 (26.8)	145.98 (33.9)	7.79 (349.0)
^{1}H-NMR	1.09 (s, 6H); 1.19 (s, 6H); 2.83 [s, 4H, $^{2}J(Sn,H) = 60.9$ Hz]; 3.28-3.49 (m, 2H); 3.89-4.11 (m, 3H); 4.15-4.34 (m, 2H); 4.40-4.60 (m, 2H); 7.00-7.60 (m [c], 32H)							
^{119}Sn-NMR	113.66							

[a] In $CDCl_3$, chemical shifts ,δ, in ppm with respect to TMS (^{1}H NMR), with respect to $CDCl_3$ central peakl (^{13}C NMR); and with respect to Me_4Sn (^{119}Sn NMR); coupling constants $^{n}J(^{119}Sn,^{13}C)$ and $^{n}J(^{119}Sn,^{1}H)$, in Hz, within brackets. [b] Other signals:128.54 (50.9), carbons b; 129.05 (11.2), carbons d; 137.05 (37.2), carbons c; 138.22 (513.8), carbons a. [c] Various very close multiplets.

The bis (1,4-disubstituted 1,2,3-triazole) **6**-**8** and **10** are all solids, and were obtained in almost quatitative yields except compound **10** (70%). Compound **6** is a yellow solid mp 275-278 °C; **7** is a pale green compound, mp 126-128 °C; **8** is a yellow solid, mp 160-162 °C; and **10** is a white amorfous product, mp 168-170 °C.

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“The authors declare no conflict of interest.”

References

1. Khan, M.F.*; Verma, Garima; Akhtar, W.*; Marella, A.; Alam, M.M; Mumtaz, A.M.; Husain, A.; Hasan, S.M.; Shaquiquzzaman, M. Haider; Syed, R. Synthetic Trends Followed for the Development of 1,2,3-Triazole Derivatives, *Int J Drug Dev & Res* 2017, *9*, 22-25.

2. (a) Kolb H.C.; Finn, M.G.; Sharpless K.B.* Click Chemistry: Diverse Chemical Function from a Few Good Reactions *Angew. Chem. Int.Ed.*, 2001, *40*, 2004-2021. doi/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5. (b) Huisgen, R.; Kinetics and reaction mechanisms: selected examples from the experience of forty years, Pure&App. Chem., 1989, *61 (4)*, 613-628.

3. Prömpers, G.; Keul, H.*; Höcker, H., Polyurethanes with pendant hydroxy groups: polycondensation of 1,6-bis-O-phenoxycarbonyl-2,3:4,5-di-O-isopropylidenegalactitol and 1,6-di-O-phenoxycarbonylgalactitol with diamines, *Green Chem.*, 2006, *8*, 467. DOI: 10.1039/b600254d

4. Rostovtsev, Vsevolod V. Dr.; Green, Luke G. Dr.; Fokin, Valery V.Prof.; Sharpless, K. Barry Prof.; A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes; Angew. Chem., Int. Ed., 2002, *41* (14), 2423-2618; https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4.