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Proceeding Paper

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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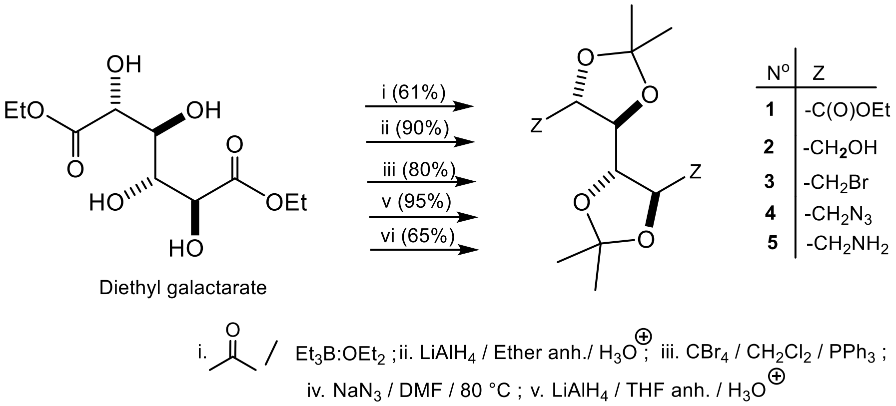
1. Introduction

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]. 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. On the other hand, our group has been engaged for some time on the synthesis of functionally substituted organotin derivatives and the study of their physical and chemical properties [2–4]. Taking into account the previous discussion, we considered it of interest to carry out the synthesis of new organotin derivatives containing 1,2,3-triazole substituentes in order to study their physical and chemical properties. We also considered possible the use of click chemistry in order to prepare 1,2,3-triazoles via cycloaddition reactions between the apropriate alkynes and azides [5]. In the present communication we report the results obtained in the first part of our project.

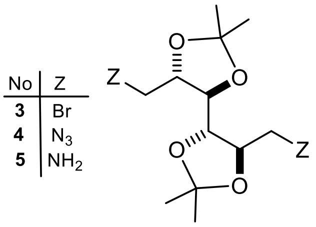
2. Results and Discussion

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 [6]. Diol **2** by reaction with CBr_4 and PPh_3 in CH_2Cl_2., gave (4R,4′S,5S,5′R)-bis(bromomethyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) (**3**) in 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. ^{1}H NMR characteristics of compounds **3**–**5** are included in Table 1.



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

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

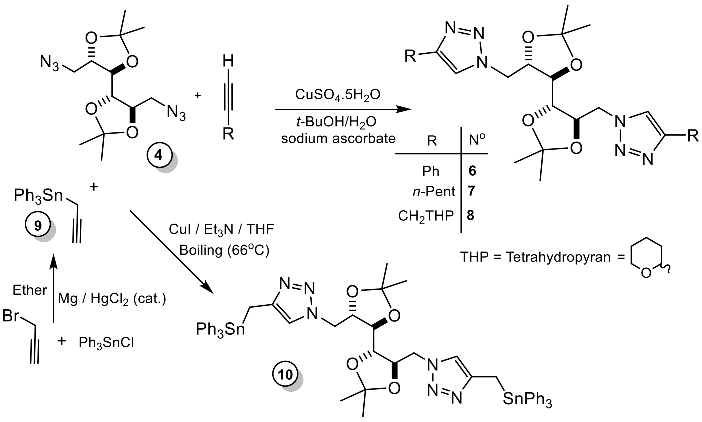


Comp. N°	**Chemical Shifts (δ, ppm)** [a]
3	1.41 (s, 6H); 1.77 (s, 6H); 3.52 (m, 2H); 3.69 (m, 2H); 3.82 (m, 2H)
4	1.31 (s, 6H); 1.38 (s, 6H); 3,22–3.28 (m, 2H); 3.56–3.62 (m, 2H); 3.70–3.73 (m, 2H); 4.03–4.09 (m, 2H)
5	1.29 (s, 6H); 1.32 (s, 6H); 2.15 (s, 4H; NH_2 x 2); 2.76 (m, 2H); 2.90 (m, 2H); 3.57 (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 [5,7]. In order to obtain molecules with two triazo substituents, we consider it of interest to explore the use of click reactions [7].

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** (0.48 mmol) 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 1 M solution), and then $CuSO_4.5H_2O$ (0.012 g, 0.050 mmol). The reaction was left overnight with stirring at RT. Then the mixture was cooled down to 0 °C, and 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.

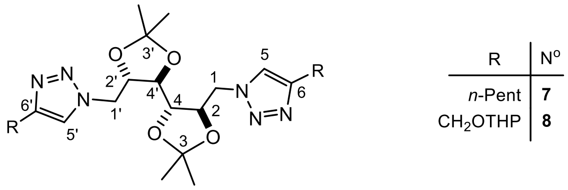


Scheme 2. Synthesis of bis (1,4-disubstituted 1,2,3-triazole) **6–8** and **10.**

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**.

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.

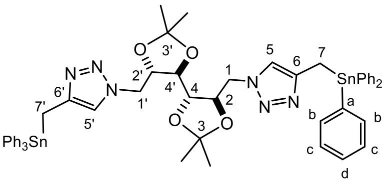
Table 2. ^{13}C-NMR characteristics of compounds 7 and 8 [a].



Comp. N°	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.

Table 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.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Khan, M.F.; Verma, G.; Akhtar, W.; Marella, A.; Alam, M.M.; Mumtaz, A.M.; Husain, A.; Hasan, S.M.; Shaquiquzzaman, M.H.; Syed, R. Synthetic Trends Followed for the Development of 1,2,3-Triazole Derivatives. *Int. J. Drug. Dev. Res.* **2017**, *9*, 22–25.
2. Zacconi, F.C.; Romina, A.; Ocampo, R.A.; Podestá, J.C.; Koll, L.C. Synthesis of organotin substituted tricyclic macrodiolides. *J. Braz. Chem. Soc.* **2016**, *27*, 484–492. https://doi.org/10.5935/0103-5053.20150275.
3. Scoccia, J.; Gerbino, D.C.; Podestá, J.C. Synthesis of new organotin substituted optically active eleven membered macrodiolides. *Tetrahedron Asym.* **2016**, *27*, 352–360. https://doi.org/10.1016/j.tetasy.2016.02.014.
4. Terraza, V.F.; Gerbino, D.C.; Podestá, J.C. *J. Organomet. Chem.* **2021**, *935*, 121680. https://doi.org/10.1016/j.jorganchem.2021.121680.
5. (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. https://doi.org/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*, 613–628.
6. 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. https://doi.org/10.1039/b600254d.
7. Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2423–2618. https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4.