

Synthesis of Bis (1,4-Disubstituted-1,2,3-triazoles) Starting from Diethyl Galactarate [†]

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[†] Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2022; Available online: <https://ecsoc-26.sciforum.net>.

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 acetone-protected diethyl galactarate (**1**). Reduction of **1** with LiAlH₄ led to dioxolane **2** (90%), which, upon treatment with CBr₄, gave the corresponding dibromide **3** (80%). The reaction of **3** with NaN₃ in DMF afforded the key diazide **4** (95%). From the diazide **4** were obtained the bis (1,4-disubstituted-1,2,3 triazoles) **5–8** via click reactions with alkyl-substituted acetylenes, including triphenyltinacetylene. The physical characteristics of the new compounds, including selected values of ¹H, ¹³C, and ¹¹⁹Sn NMR data, are given.

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



Citation: Terraza, V.; Gerbino, D.; Podestá, J. Synthesis of Bis (1,4-Disubstituted-1,2,3-triazoles) Starting from Diethyl Galactarate. *Chem. Proc.* **2022**, *12*, 22. <https://doi.org/10.3390/ecsoc-26-13689>

Academic Editor: Julio A. Seijas

Published: 17 November 2022

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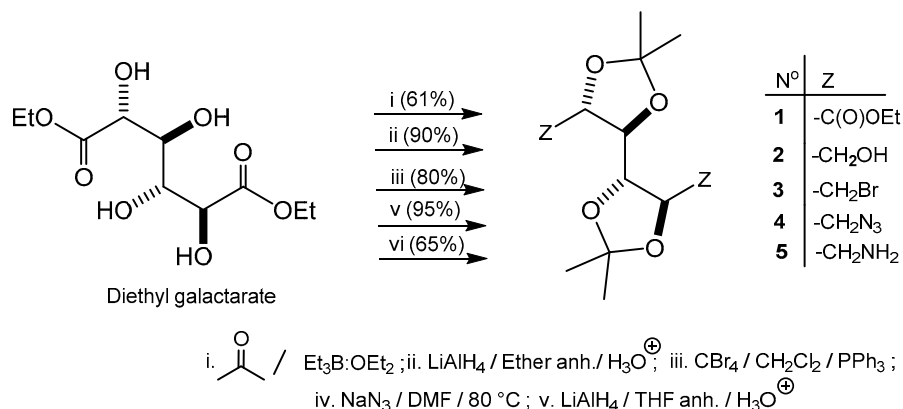
1. Introduction

As reported in many publications, 1,2,3-triazoles have found wide application in diverse areas of agriculture and medicine. The vast existing literature demonstrates the antifungal, anticonvulsant, antiviral, antibacterial, antimalarial and antidiabetic properties of these compounds [1]. Natural products, such as galactose, glucose, fructose, and manose, are useful and cheap raw materials available at an industrial scale. This makes these renewable multifunctional compounds useful for the synthesis of organic ligands, catalysts, and chiral molecules of industrial interest. 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]. In relation to the preceding discussion, we considered it of interest to carry out the synthesis of new organotin derivatives containing 1,2,3-triazole substituents to study their physical and chemical properties. We also considered the possibility of using click chemistry to prepare 1,2,3-triazoles via cycloaddition reactions between the appropriate alkynes and azides [5,6]. 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 anhydride in the presence of triethylboron etherate led to (2,3,4,5) bis-acetone-protected diethyl galactarate (**1**) in 61% yield. The reduction of **1** with LiAlH₄ 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 [7]. Diol **2** by reaction with CBr₄ and PPh₃ in CH₂Cl₂, 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 NaN₃ in DMF at 80 °C afforded (4*S*,4'*R*,5*R*,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 LiAlH₄ led to ((4 ((4*S*,4'*R*,5*R*,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. The 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.

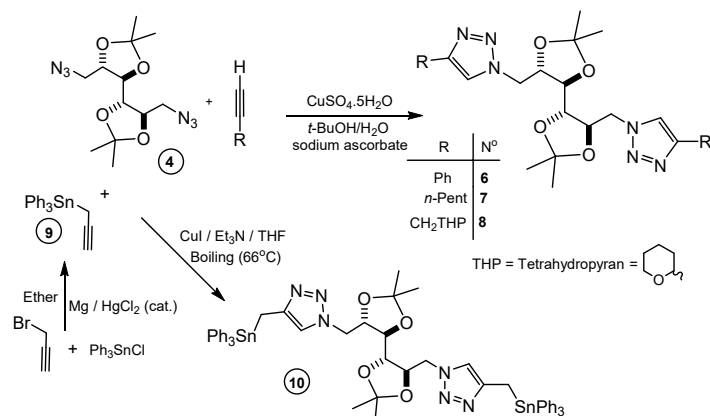
Comp. N°	Chemical Shifts (δ, ppm) ^a
3	1.41 (s, 6H); 1.77 (s, 6H); 3.52 (m, 2H); 3.69 (m, 2H); 3.82 (m, 2H)
4	1.31 (s, 6H); 1.38 (s, 6H); 3.22–3.28 (m, 2H); 3.56–3.62 (m, 2H); 3.70–3.73 (m, 2H); 4.03–4.09 (m, 2H)
5	1.29 (s, 6H); 1.32 (s, 6H); 2.15 (s, 4H; NH ₂ × 2); 2.76 (m, 2H); 2.90 (m, 2H); 3.57 (m, 2H); 3.90 (m, 2H)

^a In CDCl₃. Chemical shifts with respect to TMS.

1,3-Dipolar cycloaddition, usually referred to as Huisgen cycloaddition, is one of the most powerful methods for the preparation, in excellent yields, of 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 considered it of interest to explore the use of click reactions [8].

In this communication, we inform the synthesis of some bis (1,4-disubstituted 1,2,3-triazoles) using diazide **4** as a starting material. The reactions were carried out by preparing a suspension of **4** (0.48 mmol) and the terminal alkyne (0.97 mmol) in a 1:1 mixture of t-butanol/water (2 mL). To the suspension was added sodium ascorbate (0.05 mL of an aqueous 1 M solution) and then CuSO₄·5H₂O (0.012 g, 0.050 mmol). The reaction was left overnight with stirring at RT. Then the mixture was cooled to 0 °C and water (0.50 mL) was added. The formation of a precipitate was observed, which was filtered giving the desired products in all cases with almost quantitative yields. In Scheme 2, the synthesis of bis (1,4-disubstituted 1,2,3-triazole) **6**–**8** and **10** is shown. For the synthesis of organotin derivative **10**, using the combination sodium ascorbate/CuSO₄ in water, no reaction was observed. However, the reaction using CuI and Et₃N in THF and under reflux gave 1,1'-(4*R*,4'*S*,5*S*,5'*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane)]-5,5'-diylbis(methyle)bis [4-

(triphenylstannyl)methyl)-1*H*-1,2,3-triazol] (10), which was purified by column chromatography. Compound 6 is not soluble in common NMR solvents and 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 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 HgCl₂ (Scheme 2). The ¹³C NMR characteristics of compounds 7 and 8 are summarized in Table 2. The ¹³C, ¹H and ¹¹⁹Sn NMR characteristics of compound 10 are listed in Table 3.

Table 2. ¹³C-NMR characteristics of compounds 7 and 8 ^a.

	R	N°
	<i>n</i> -Pent	7
	CH ₂ OTHP	8

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 CDCl₃, chemical shifts, δ , in ppm with respect to CDCl₃ central peak; ^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. ¹³C-, ¹H and ¹¹⁹Sn 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 CDCl₃, chemical shifts, δ , in ppm with respect to TMS (¹H NMR), with respect to CDCl₃ central peak (¹³C NMR); and with respect to Me₄Sn (¹¹⁹Sn NMR); coupling constants ⁿJ(¹¹⁹Sn, ¹³C) and ⁿJ(¹¹⁹Sn, ¹H), 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 compounds bis (1,4-disubstituted 1,2,3-triazole) **6–8** and **10** are all solids and were obtained in almost quantitative yields, except for compound **10** (70%). Compound **6** is a yellow solid, m.p. 275–278 °C; **7** is a pale green compound, m.p. 126–128 °C; **8** is a yellow solid, m.p. 160–162 °C; and **10** is a white amorphous product, m.p. 168–170 °C.

Author Contributions: Conceptualization, J.P.; methodology, V.T., J.P. and D.G.; Analysis, V.T., J.P. and D.G.; Resources, J.P.; writing—original draft preparation, J.P.; writing—review and editing, J.P. and V.T.; supervision, J.P. and D.G.; project administration, J.P.; funding acquisition, J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by ANPCYT, Capital Federal, Argentina/BID, PICT project N° 2644; CONICET, project PIP N° 11220110100828; Universidad Nacional del Sur, Bahía Blanca, Argentina, project PGI N° 24/Q069.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: This research was funded by ANPCYT, Capital Federal, Argentina/BID, PICT project N° 2644; CONICET, project PIP N° 11220110100828; Universidad Nacional del Sur, Bahía Blanca, Argentina, project PGI N° 24/Q069. CONICET, ANPCyT, and UNS of Argentina supported this work. A fellowship from CIC-PBA (Argentina) to VFT (Leg. N° 6587) is gratefully acknowledged.

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

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