

Synthesis of 1,1'-methylenebis(1,2,4-triazole) functionalized in the methylene bridge. A new approach to dendrons bearing heterocyclic rings on the periphery

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Dedicated to Professor José Elguero on the occasion of his 70th birthday
and to Professor Pedro Molina on the occasion of his 60th birthday

(received 23 Dec 04; accepted 25 Feb 05; published on the web 13 Mar 05)

Abstract

3,3-Bis(1,2,4-triazol-1-yl)-1-propanol was obtained by reduction of its methyl carboxylate derivative. This compound is able to form the first generation dendron containing two bis(1,2,4-triazol-1-yl)methyl systems on the periphery by reaction of its mesylate derivative with 3,5-dihydroxybenzyl alcohol.

Keywords: Heterocyclic dendrons, 1,2,4-triazole, polyethers

Introduction

1,1'-Methylenebis(1,2,4-triazole) is a useful compound in coordination chemistry owing to its ability to form *N,N*-complexes¹ and biscarbenes that are able to coordinate transition metals.² Functionalization of the methylene bridge would enable this compound to be transformed into bidentate ligands with a focal group, which should allow this structure to be incorporated into different macromolecules such as polymers or dendrimers. Although several methodologies have been described for the preparation of bridge-functionalized 1,1'-methylenedipyrzole and 1,1'-methylenediimidazole,³ the use of these systems in the synthesis of 1,2,4-triazole derivatives still remains a desirable goal. To the best of our knowledge, only two such examples have been described and these are 4-[bis(1,2,4-triazol-1-yl)methyl]phenol⁴ (**1**) and methyl 3,3-bis(1,2,4-triazol-1-yl)propionate³ (**2**). Compound **1** was coupled to 1,3,5-tris(chlorocarbonyl)benzene to give a system that is a precursor for *N*-heterocyclic carbenes (NHC). However, further exploitation of this compound was not possible, probably due to the ease with which the benzylic methine bearing two triazole rings can be cleaved.⁵ For this reason we chose compound **2**, in

which the presence of a benzylic position has been avoided in order to perform convergent dendritic growth using a Fréchet methodology.⁶ Thus, transformation of the ester group into either a bromide or sulfonate derivative - both of which can be efficiently substituted by phenoxy groups - is necessary.

In this paper we describe the synthesis of hydroxyl, bromide and mesylate (**3**, **4** and **5**) derivatives starting from the aforementioned ester **2**. The coupling of mesylate **5** with 3,5-dihydroxybenzyl alcohol to give the first generation dendron **7** is also described.

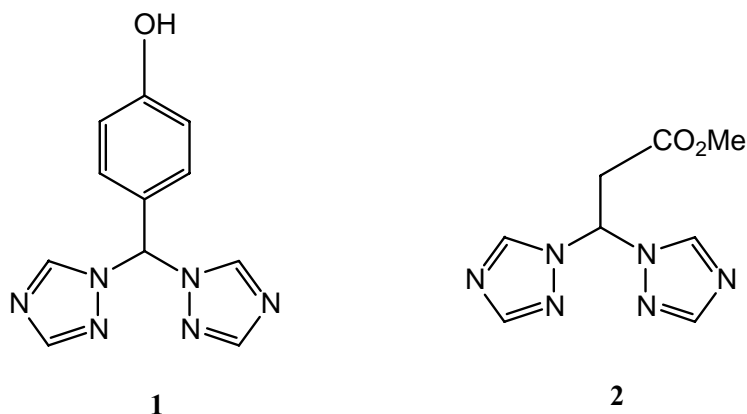
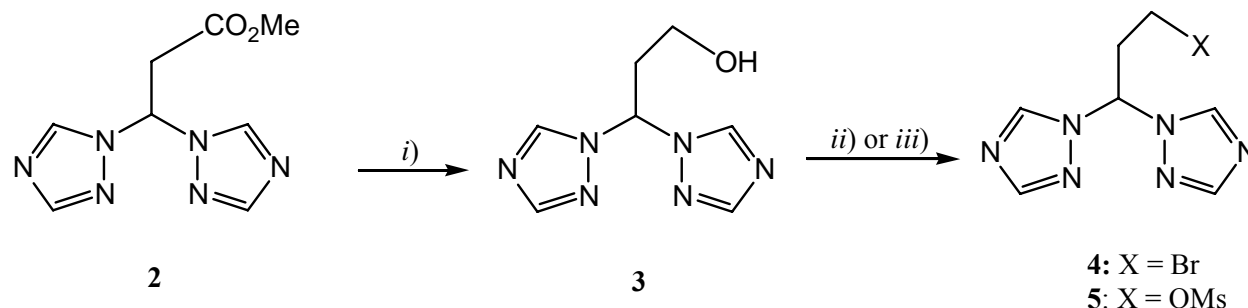


Figure 1

Results and Discussion

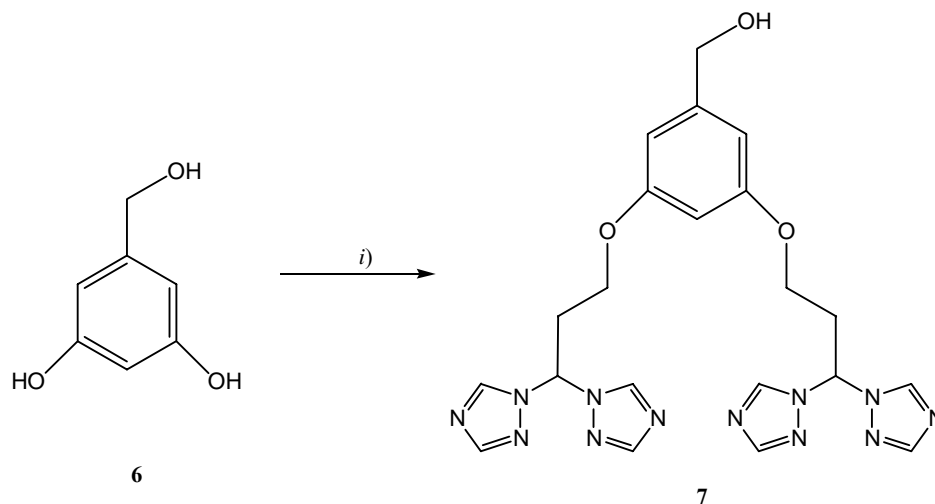
Methyl 3,3-bis(1,2,4-triazol-1-yl)propionate (**2**) was obtained by a double Michael addition of 1,2,4-triazole to methyl propiolate.³ Attempts to reduce the ester group using lithium aluminum hydride in refluxing THF or borane-methyl sulfide complex resulted in complete decomposition of the starting materials. However, 3,3-bis(1,2,4-triazol-1-yl)propanol (**3**) could be obtained in good yield (70%) using a large excess of lithium aluminum hydride in THF at -60 °C for 25 min. (Scheme 1). Evidence for the formation of **3** was provided by ¹H NMR spectroscopy. The spectrum did not contain a signal for a methyl group and two doublet of triplets were observed at 3.60 and 2.84 ppm, which are assigned to the protons of the two methylene groups (coupling with the hydroxylic proton is observed).

The bromide derivative **4** was prepared by treatment of alcohol **3** with 4 equivalents of carbon tetrabromide and 4 equivalents of triphenylphosphine in acetonitrile at rt for 24h. Purification of the product proved difficult and it could only be obtained in moderate yield (maximum 40%). On the other hand, the hydroxyl group of **3** was transformed into the corresponding mesylate derivative in 96% yield by reaction with 1.5 equivalents of MsCl and Et₃N in THF at rt for 2h. A ¹H NMR signal at 3.03 ppm - assigned to the methyl group in the spectrum of **5** - supports the structure of this product.



Scheme 1. (i) LiAlH_4 (excess), THF, $-60\text{ }^\circ\text{C}$, 25 min, then H_2O , 70%. (ii) CBr_4 (4 eq), PPh_3 (4 eq), CH_3CN , rt, 24 h, 40%. (iii) MsCl (1.5 eq), Et_3N (1.5 eq), THF, rt, 2 h, 96%.

The first generation dendron **7** was obtained in 75% yield by reaction of **5** with 0.5 equivalents of 3,5-dihydroxybenzyl alcohol using an excess of potassium carbonate and a catalytic amount of 18-crown-6 (18-C-6) (Scheme 2) in THF refluxed for 16h.. The ^1H NMR spectrum of **7** contained a doublet at 6.46 ppm and a triplet at 6.22 ppm. These signals are assigned to the protons of the benzene ring. The peaks due to the two branches appear as one group of signals and this observation is consistent with a symmetric structure. The protons of the triazole rings and the hydrogen of the bridge have chemical shifts similar to those of **3**, although the signals for the aliphatic protons of the side arms are observed at higher chemical shifts. The signal for the benzylic protons appears at 4.61 ppm as a singlet. The structure of this compound was also confirmed by ^{13}C NMR spectroscopy. The spectrum contains signals at 100.6 and 105.5 ppm for the *para* and *ortho* carbons, respectively, and 159.2 and 144.1 for the *ipso* and *meta* carbons of the benzene ring. A peak for the molecular ion was observed at m/z 492.2 (EI-MS) and matches the calculated molecular mass.



Scheme 2. i) **5** (0.5 eq), K_2CO_3 (excess), 18-C-6 (cat.), THF, reflux, 16 h, 75%.

Conclusions

A first generation dendron containing two bis(1,2,4-triazol-1-yl)methyl systems on the periphery can be prepared by reaction of mesylate **5** with 3,5-dihydroxybenzyl alcohol.

Experiments involving the further elaboration of dendron **7** in the synthesis of poly(*N*-heterocyclic carbenes) are now in progress in our laboratories.

Experimental Section

General Procedures. Solvents were purified by distillation from appropriate drying reagents before use. All reagents were used as received and without further purification. When necessary, work was carried out using standard Schlenk techniques under an atmosphere of dry argon. Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 CHN microanalyzer. Electron Impact (EI) (working at 70 V and 200 °C) experiments were performed on a VG Autospec instrument belonging to Servicio Interdepartamental de Investigación, Universidad Autónoma de Madrid. IR spectra were recorded on a Nicolet 550 spectrophotometer (FT-IR). NMR spectra were recorded in CDCl₃ on a Varian Inova-500 instrument with TMS or the solvent carbon signal as the standards, operating at 500 MHz for ¹H and 125 MHz for ¹³C. Chemical shift are expressed in parts per million (δ). The signals were assigned with the help of difference NOE and Hetcor experiments.

3,3-Bis(1,2,4-triazol-1-yl)-1-propanol (3). A solution of **2** (2.50 g, 11.25 mmol) in THF (50 mL) was slowly added to a mixture of LiAlH₄ (533 mg, 14.04 mmol) and THF (5 mL) at -60 °C. The reaction mixture was stirred at that temperature for 25 min. The excess LiAlH₄ was hydrolyzed by careful addition (dropwise) of water (300 μL). The cooling bath was then removed and the solution allowed to warm up to room temperature. The solution was concentrated under vacuum until the volume was 20% of the original volume. The resulting material was centrifuged and decanted. The remaining white solid was stirred with several portions of THF (3 × 20 mL) in order to extract the maximum amount of the absorbed product. The combined organic extracts were dried over Na₂SO₄ and the solvent removed under vacuum to afford the title alcohol **3** as a yellow oil. The pure product was obtained as a colorless solid after crystallization from CHCl₃. Yield 70%. mp 128-130 °C. IR (KBr, cm⁻¹): 3276 (O-H), 1504, 1282, 1135. ¹H NMR: 1.86 (t, *J* = 4 Hz, 1H, OH), 2.84 (dt, *J* = 5.8 Hz, 7.4 Hz, 2H, CH₂CH₂OH), 3.60 (dt, *J* = 5.8 Hz, 4.7 Hz, 2H, CH₂OH), 6.95 (t, *J* = 7.4 Hz, 1H, CHTz₂), 7.98 [s, 2H, H3 (Tz)], 8.39 [s, 2H, H5 (Tz)]. ¹³C NMR: 35.9 (CH₂CH₂OH), 57.1 (CH₂OH), 68.7 (CHTz₂), 142.9 [C5 (Tz)], 152.4 [C3 (Tz)]. MS (EI), *m/z*: 150, 176.0 [M-H₂O]⁺. Anal. Calc. for C₇H₁₀N₆O (194.19): C, 43.29; H, 5.19; N, 43.28%. Found: C, 43.09; H, 5.08; N, 43.47%.

1,1'-(3-Bromopropylidene)bis(1,2,4-triazole) (4). To a solution of **3** (400 mg, 2.06 mmol) and carbon tetrabromide (2.73 g, 8.24 mmol) in acetonitrile (30 mL) was added a solution of triphenylphosphine (2.16 g, 8.24 mmol) in acetonitrile (20 mL). The reaction mixture was stirred under argon for 24 h at room temperature. Potassium carbonate (1 g) was added and stirring was maintained until the organic layer had been neutralized (15 min). The crude mixture was filtered and the solvent evaporated under vacuum. The residue was purified by chromatography (SiO₂, hexanes/ethyl acetate, 1:10) followed by crystallization from CH₂Cl₂/Et₂O. Compound **4** was obtained as a colorless solid. Yield 40%. mp 122-124 °C. IR (KBr, cm⁻¹): 1504, 1435, 1282. ¹H NMR: 3.15 (pseudo-q, *J* = 6.20 Hz, 2H, CH₂CH₂Br), 3.28 (t, *J* = 5.9 Hz, 2H, CH₂Br), 6.97 (t, *J* = 7.3 Hz, 1H, CHTz₂), 8.01 [s, 2H, H3 (Tz)], 8.42 [s, 2H, H5 (Tz)]. ¹³C NMR: 26.77 (CH₂Br), 35.6 (CH₂CH₂Br), 69.9 (CHTz₂), 143.2 [C5 (Tz)], 152.8 [C3 (Tz)]. MS (EI), *m/z*: 256.0 [M]⁺, 258.0 [M+2]⁺. Anal. Calc. for C₇H₉BrN₆ (257.09) C, 32.70; H, 3.53; N, 32.69%. Found: C, 32.43; H, 3.21; N, 32.87%.

3,3-Bis(1,2,4-triazol-1-yl)-1-propyl mesylate (5). A stirred mixture of **3** (200 mg, 1.03 mmol) and Et₃N (215 μL, 1.55 mmol) in THF (40 mL) was cooled to 0 °C and treated dropwise with a solution of freshly distilled MsCl (177 mg, 1.55 mmol) in THF (10 mL). The mixture was allowed to warm up to room temperature for a further 2 h. Et₃N·HCl was then removed by centrifugation and the solvent evaporated under vacuum. Compound **5** was obtained as an oil after chromatography (SiO₂, CH₂Cl₂/EtOH, 25:1). Yield 96%. IR (THF, cm⁻¹): 1506, 1417, 1376, 1346. ¹H NMR: 3.03 (s, 3H, CH₃), 3.10 (dt, *J* = 5.5 Hz, 7.3 Hz, 2H, CH₂CH₂O), 4.21 (t, *J* = 5.5 Hz, 2H, CH₂O), 6.87 (t, *J* = 7.3 Hz, 1H, CHTz₂), 8.01 [s, 2H, H3 (Tz)], 8.40 [s, 2H, H5 (Tz)]. ¹³C NMR: 33.6 (CH₂CH₂O), 37.6 (CH₃), 64.0 (CH₂CH₂O), 68.0 (CHTz₂), 143.3 [C5 (Tz)], 152.9 [C3 (Tz)]. MS (EI), *m/z*: 272.1 [M]⁺.

Dendron 7. A mixture of **5** (150 mg, 0.55 mmol), 3,5-dihydroxybenzyl alcohol (39 mg, 0.27 mmol), dry potassium carbonate (208 mg, 1.50 mmol) and 18-crown-6 (5 mg, 0.02 mmol) in dry THF (15 mL) was heated under reflux and stirred vigorously under argon for 16 h. The mixture was allowed to cool to room temperature, filtered and evaporated to dryness under reduced pressure. The crude product was purified by chromatography (SiO₂, CH₂Cl₂/EtOH, 25:1) followed by crystallization from CH₂Cl₂/CCl₄ to give **7** as a colorless solid. Yield 75%. mp: 140-142 °C. ¹H NMR: 3.10 (q, *J* = 5.5 Hz, 4H, CH₂CH₂O), 3.68 (s, 1H, OH), 3.89 (t, *J* = 5.3 Hz, 4H, CH₂CH₂O), 4.61 (s, 2H, CH₂OH), 6.22 (t, *J* = 2.2 Hz, 1H, CH-*para*), 6.46 (d, *J* = 1.8 Hz, 2H, CH-*ortho*), 6.98 (t, *J* = 5 Hz, 2H, CHTz₂), 8.00 [s, 4H, H3 (Tz)], 8.41 [s, 4H, H5 (Tz)]. ¹³C NMR: 33.4 (CH₂CH₂O), 62.4 (CH₂CH₂O), 64.8 (CH₂OH), 68.6 (CHTz₂), 100.6 (C-*para*), 105.5 (C-*ortho*), 143.1 [C5 (Tz)], 144.1, 152.7 [C3 (Tz)], 159.2. MS (EI), *m/z*: 492.2 [M]⁺.

Acknowledgements

This work was supported by the Consejería de Educación y Ciencia de Castilla-La Mancha (Projects PAI-02-016 and GC-02-013). J. G. is indebted to the Junta de Comunidades de Castilla-La Mancha for a grant.

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