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RESEARCH ARTICLE

Precursor Synthesis of Some New Macrocyclic Compounds

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Objective: Development of new electronic devices with applications in computer science as well as new medical devices pushed the researcher to find new technologies. Based on those new techniques we have designed and synthesized compounds with possible application in the field of advanced materials. **Material and method:** Compounds were analyzed by TLC and NMR. Routine 1H NMR (250 MHz) spectra were recorded at room temperature in deuterated acetone, unless stated otherwise. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silicagel 60 F254 Merck TLC plates. **Results:** Starting from commercial available compounds intermediates were obtained in a good yield. 4,4'-(2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diyl)diphenol was obtained starting from pentaerythritol and p-hydroxy-benzaldehyde in the presence of catalytic amounts of APTS (p-toluensulfonic acid). The product was purified by recrystallization and characterized by NMR spectroscopy. The structure exhibit 2 different signals for equatorial and axial position. Furthermore di, tri and tetra ethylene glycol were obtained by microwave assisted synthesis in a matter of minutes. Compounds were separated by recrystallization. **Conclusions:** In conclusion, several intermediates were synthesized and characterized from spectroscopic point of view. Further analyses should be carried out and the compounds should be tested as advanced materials.

Keywords: spiran, 1,3-dioxan, polyethylene glycol, inside&outside methylene group

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Introduction

Macrocyclic compound played a major role in the field of supramolecular chemistry because they can form organized supramolecular assemblies. Usually these macrocyclic have cavity of different size and can accommodate small or large molecules by host-guest interactions [1].

The design and synthesis of new macrocyclic compounds remain of great interest due to wide applications such as catalysis [2-4], advanced materials [5-7] and medicine [8-11].

One narrow domain of supramolecular chemistry is the field of molecular machine. Such as cars are driven by the conversion of piston action into a rotary motion, there are molecules that can undergo programmed motions in response to different stimuli. Molecular analogues of a variety of mechanical devices such as molecular rocking chair [12], rudder, wringer [13], shuttles [14], molecular elevator [15], unidirectional rotors [16], and tweezers have been created. But these "molecular machines" have been controlled by structural transition between two or more stable states in a reversible manner by one single moiety using external stimuli such as light, temperature or pH.

The aim of our work was the design and synthesis of some precursors of some macrocyclic compounds which incorporate 2 different switchable units and can be valuable compounds for synthesis of new photochemically and conformational controlled molecular devices. Converting light-energy in "molecular motion" by *cis-trans* isomerization is one of the most studied and applied system by researchers. Usually azobenzene [17] or stilbene [18] derivatives are used due to the possibility of controlling the isomerization by both UV light and thermal relaxation [19]. Photoisomerization of azobenzene derivatives have been used to control electronic properties of more complex compounds [19] or to drive the folding/unfolding of peptide chains [20]. Therefore, we have considered of great interest the synthesis of some intermediates as building blocks for new macrocycles which can incorporated two or more switchable units.

Material and methods

All reagents were acquired from Sigma Aldrich, Merck or Alfa Aesar and were used without any further purification. Routine ^{1}H NMR (250 MHz) were recorded at room temperature (r.t.) in CD_3COCD_3, unless stated otherwise on a Bruker 250 MHz spectrometer, using the solvent line as reference. Chemical shifts (δ) are reported in parts per million (ppm) values using residual solvent peak as internal reference and the coupling constants (J) are in Hertz (Hz). Multiplicities are abbreviated as: *s*-singlet; *d*-doublet; *dd*-doublet of doublet; *t*-triplet; *q*-quadruplet and *m*-multiplet. Compounds were analyzed by TLC and NMR. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silicagel 60 F_{254} Merck TLC plates.

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Melting points were determined using a Boetius microscope and represent uncorrected values.

The irradiation was carried out in a domestic microwave oven (Samsung, model MS23F301EAK).

Synthesis of 3,3'-(2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diyl)diphenol (3)

A mixture of 3-hydroxybenzaldehyde (1.22 g, 1 mmol), pentaerythritol (680 mg, 0.5 mmol) and paratoluensulfonic acid (38 mg, 0.2 mmol) were stirred under reflux in a two-necked glassware flask connected to a Dear-Stark apparatus in about 100 mL toluene. The reaction was monitored by thin layer chromatography on silica gel coated plates Merck 30-F_{254} using pentane:ethylacetate mixture (9:2 v/v). After completion of the reaction the mixture was washed three times with water, dried over Na_2SO_4, and filtered. Evaporation of the solvent in vacuo gave the desired crude product. The product was purified furthermore by recrystallization from ethanol (yield: 23%, mp 243-247 °C). ^{1}H NMR (250 MHz, CD_3COCD_3) δ/ppm 2.62 (dd, *J*=11.7 Hz, *J'*=1.8 Hz, 2H, H_{eq}); 3.01 (m, 2H, H_{ax}); 3.33 (d, *J*=11.7 Hz, 2H, H_{ax}); 4.15 (dd, *J*=11.7 Hz, *J'*=1.8 Hz, 2H, H_{eq}); 5.23 (s, 2H, Ar-C*H*); 6.80 (overlapped, 2H, H-6', H-6"); 6.94-7.07 (m, 4H, H-2', H-2" and protons H-4', H-4"); 7.18 (overlapped dd, 2H, H-5', H-5"); 8.70 (s, 1H, O*H*).

General procedure for synthesis of di-, tri- and tetraethylene glycol ditosylate

All compounds were obtained using a modified procedure described by Kazemi and coworkers [21]. 10.13 g K_2CO_3 (73.42 mmol), 50 mmol alcohol and 13.24 g (69.5mmol) p-toluenesulfonyl chloride were charged into a mortar and grinded vigorously for about 15 minutes. A small amount of the mixture was dissolved in dichloromethane and the reaction progress was monitored by thin layer chromatography on silica gel coated plates Merck 30-F254) using dichloromethane:pentane mixture (1:2 v/v). The excess of tosyl chloride was removed by addition of about 2 mL of *t*-BuOH and irradiated (600 W) in a domestic microwave for about 3 minutes (*caution: a smoke was generated during the irradiation; therefore, the entire process was carried out under a very good ventilated chemical hood*). The reaction mixture was stirred with ethylic ether washed twice with small portion of brine and the combined organic layers were dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. The crude product either purified by recrystallization or by flash-chromatography (using a mixture of pentane:dichloromethane as eluent) affording pure tosylated compound.

Diethyleneglycol ditosylate (6a): Colorless crystals: m.p. 86-89°C. Yield: 87%. ^{1}H NMR (250 MHz, $CDCl_3$) δ/ppm 2.46 (s, 6H, CH_3); 3.63 (t, 4H, OCH_2); 4.11 (t, 4H, OCH_2); 7.35 (d, 4H, H-3', H-3"); 7.76 (d, 4H, H-2', H-2");

Triethyleneglycol ditosylate (6b): Colorless crystals: m.p. 76-80°C. Yield: 88%. ^{1}H NMR (250 MHz, $CDCl_3$) δ/ppm 2.31 (s, 6H, CH_3); 3.45 (s, 4H); 3.56 (t, 4H, OCH_2); 4.02 (t, 4H, OCH_2);7.26 (d, 4H, H-3', H-3"); 7.69 (d, 4H, H-2', H-2");

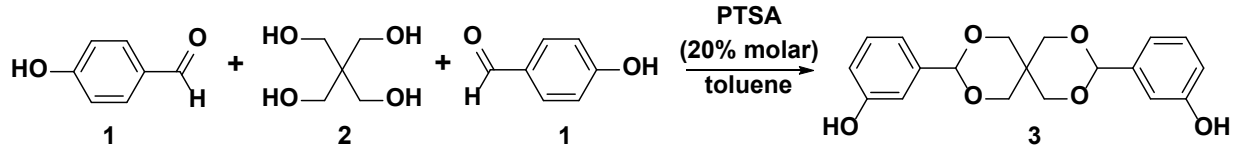
Tetraethyleneglycol ditosylate (6c): Tick oil. Yield: 84%. ^{1}H NMR (250 MHz, $CDCl_3$) δ/ppm 2.22 (s, 6H, CH_3); 3.38 (m, 8H); 3.45 (t, 4H, OCH_2); 3.96 (t, 4H, OCH_2);7.16 (d, 4H, H-3', H-3"); 7.58 (d, 4H, H-2', H-2");

Results

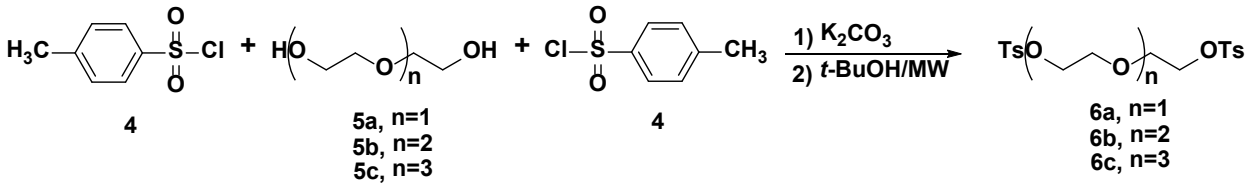
Since molecular devices are nowadays mostly controlled by mean of UV light we have thought that also conformational changes can be a way of controlling nanoscale devices. Therefore, we have designed a macrocyclic compound that bears both a spiran unit and a azobenzene moiety linked by polyethylene glycol linkage. In the first step, we have synthesized the spiran unit starting from commercially available reagents (scheme 1) in the presence of para-toluene sulfonic acid (PTSA) as catalyst.

Spiran 3 was characterized by NMR spectroscopy and melting point was determined using a Boetius microscope. Both melting point [22] and NMR are in accordance with literature data.

Also, we have synthesized 3 polyethylene glycol ditosylate starting from corresponding alcohol and tosyl chloride in a manner of minutes using a solvent-free modified method described previously in the literature by Kazemi and coworkers [21] (Scheme 2).



Scheme 1.

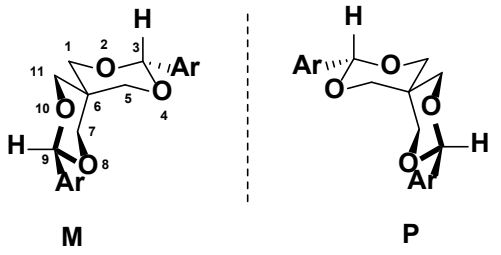


Scheme 2.

Discussions

Since saturated six membered ring are one of the most studied class of compounds regarding the conformational changes we had in mind the design and synthesis of some macrocyclic compounds bearing this moiety. Since we intended to have a friendly green synthesis we have avoid using toxic solvents in the synthesis and we have tried to obtain the compound 3 following a method described in the literature [23] using a domestic microwave. Unfortunately, after irradiation in a domestic microwave an insoluble black tar was obtained. Therefore, we have followed classical method of synthesis of diacetals using acidic conditions (scheme 1).

Aryl derivatives of 2,4,8,10-tetraoxaspiro[5.5]undecane have specific helical and axial chirality [24]. On the other hand, 1,3-dioxane rings have an anancomeric structure where the conformational equilibrium is strongly shifted towards the conformer where aryl groups are in equatorial position. Due to the spiro skeleton which exhibit helical chirality, under reaction condition, the product is a racemic mixture of both M and P helix configuration [24] (Scheme 3).



Scheme 3. (reprinted from Grosu et al., 2003 [22], with permission from Wiley)

Because of this conformational arrangement, NMR spectrum of compound 3 exhibit different signals for axial and equatorial protons from positions 5 and 7, as well as protons from positions 1 and 11. Methylene from positions 5 and 7 are oriented towards the other 1,3-dioxane ring, being called methylene inside. The other two positions (1 and 11) which are oriented in the opposite direction are called methylene outside [25]. All the protons from spiran skeleton exhibit two AB (AX) systems. Also, a long-range coupling split supplementary the equatorial protons. This was happened because of a "W (M)" arrangement of the bonds in a way of H_{eq}– $C^{1(11)}$–C^{6}–$C^{5(7)}$–H_{eq} between equatorial positions, therefore the signals for protons form equatorial positions are seen as doublets of doublets (figure 1).

Also, the equatorial protons of the methylene inside positions are more deshielded than those of outside position.

Furthermore, three ditosylated polyethylene glycol were synthesized using a very convenient solvent-free method,

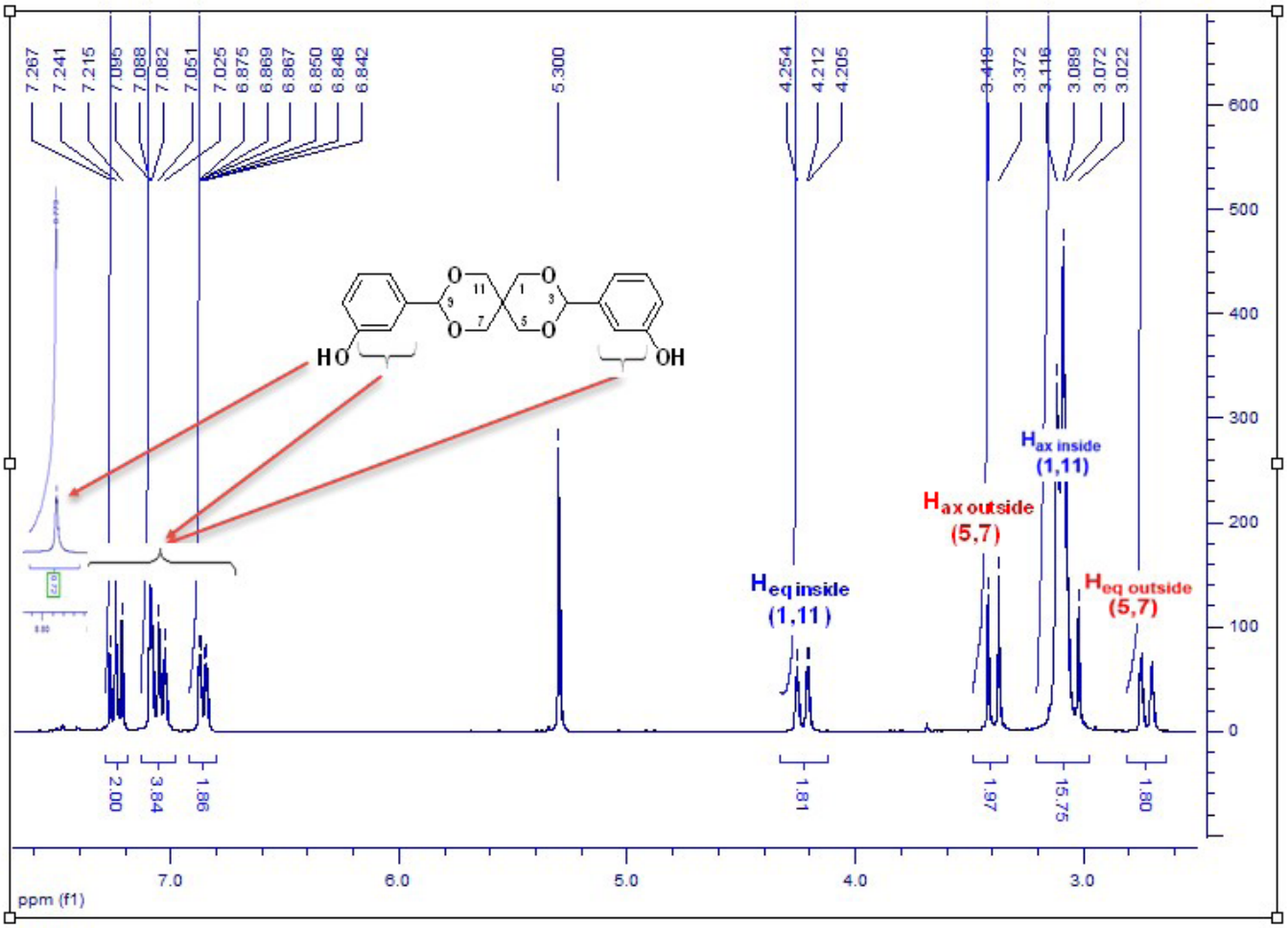


Figure 1 ^{1}HNMR spectrum (Acetone-D_6, rt) of compound 3

starting from alcohol and tosyl chloride in basic media. Reaction is very quick and occur in very good yield.

Conclusions

In conclusion, we have synthesized and characterized one spiran showing different signals in NMR spectra for equatorial and axial positions. Also, due to spatial conformation of the spiran skeleton differences occur between inside and outside methylene protons in ^{1}H-NMR. Di-, tri- and tetra glycol ditosylated were obtained in good yield in a solvent-free condition.

Acknowledgements

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Conflict of interest

None to declare.

References

1. Ogoshi T – Pillarenes, in Gale P, Steed J (eds): Monographs in Supramolecular Chemistry no. 18, Royal Society of Chemistry, Cambridge, UK, 2016, 1-3;
2. Madhavan N,Takatani T, Sherrill CD, Weck M – Macrocyclic cyclooctene-supported AlCl-salen catalysts for conjugated addition reactions: effect of linker and support structure on catalysis. Chem Eur J. 2009;15:1186-1194;
3. Grossmann A, Bartlett S, Janecek M, Hodgkinson JT, Spring DR – Diversity-oriented synthesis of drug-like macrocyclic scaffolds using an orthogonal organo- and metal catalysis strategy. Angew Chem Int Ed. 2014;53:13093-13097;
4. Li ZP, Liu BH – The use of macrocyclic compounds as eletrocatalysts in fuel cells. J Appl Electrochem. 2010;40:475-483;
5. Prasanna deSilva A – Molecular logic-based computation, in Gale P, Steed J (eds): Monographs in Supramolecular Chemistry no. 12, Royal Society of Chemistry, Cambridge, UK, 2012, 35-36;
6. Ballardini R, Balzani V, Credi A, Gandolfi MT; Kotzyba-Hilbert F, Lehn J-M, Prodi L – Supramolecular Photochemistry and Photophysics. A Cylindrical Macrotricyclic Receptor and its Adducts with Protons, Ammonium Ions, and a Pt(II) Complex. J Am Chem Soc. 1994;116:5741-5746;
7. Jyothi RK, Lee JY – The role of macrocyclic compounds in the extraction and possible separation of platinum and rhodium from chloride solutions. Sci Rep. 2016;6;27668:1-14;
8. You L, An R, Liang K, Cui B, Wang X – Macrocyclic Compounds: Emerging Opportunities for Current Drug Discovery. Curr Pharm Des. 2016;22:4086-4093;
9. Mallinson J, Collins I – Macrocycles in new drug discovery. Future Med Chem. 2012;4:1409-1438;
10. Ning CQ, Lu C, Yu NF et al. – Macrocyclic compounds as anti-cancer agents: Design and synthesis of multi-acting inhibitors against HDAC, FLT3 and JAK2. Eur J Med Chem. 2015;95:104-115;
11. Wanninger S, Lorenz V, Subhan A, Edelmann FT – Metal complexes of curcumin -synthetic strategies, structures and medicinal applications. Chem Soc Rev. 2015;44:4986-5002;
12. Balog M, Grosu I, Ple G, Ramondenc Y, Condamine E, Varga RA – Design and Synthesis of New Macrocyclic Cyclophanes Using 1,3-Dioxane Units as Bridges: A Molecular "Rocking Chair". J Org Chem. 2004;69:1337-1345;
13. Bogdan N, Grosu I, Benoit G, Toupet L, Ramondenc Y, Condamine E, Silaghi-Dumitrescu I, Ple G – Molecular Rotors: Design, Synthesis, Structural Analysis, and Silver Complex of New [7.7]Cyclophanes. Org Lett. 2006;8:2619-2622;
14. Collin JP, Dietrich-Buchecker C, Gaviña P, Jimenez-Molero MC, Sauvage JP – Shuttles and Muscles: Linear Molecular Machines Based on Transition Metals. Acc Chem Res. 2001;34:477-487;
15. Badjic JD, Balzani V, Credi A, Silvi S, Stoddart JF – A Molecular Elevator. Science. 2004;303:1845-1849;
16. Leigh DA, Wong JKY, Dehez F, Zerbetto F – Unidirectional rotation in a mechanically interlocked molecular rotor. Nature. 2003;424:174-179;
17. Kocsis I, Hădade N, Grosu I – Synthesis and structural analysis of some new arylbromide decorated azobenzene derivatives. Studia UBB Chemia. 2012;LVII(4):101-107;
18. Liu F, Morokuma K – Computational study on the working mechanism of a stilbene light-driven molecular rotary motor: sloped minimal energy path and unidirectional nonadiabatic photoisomerization. J Am Chem Soc. 2012;134:4864-4876;
19. Merino E, Ribagorda M – Control over molecular motion using cis-trans photoisomerization of the azo-group. Beilstein J Org Chem. 2012;8:1071-1090;
20. Xia SH, Cui G, Fang WH, Thiel W – How photoisomerization drives peptide folding and unfolding: Insights from QM/MM and MM dynamics simulations. Angew Chem Int Ed. 2016;55:2067-2072;
21. Kazemi F, Massah AR, Javaherian M – Chemoselective and scalable preparation of alkyl tosylates under solvent-free conditions. Tetrahedron. 2007;63:5083-5087;
22. Grosu I, Bogdan E, Plé G, Toupet L, Ramondenc Y, Condamine E, Peulon-Agasse V, Balog M – Synthesis and structure of a new macrocycles including spiro-1,3-dioxane units. Eur J Org Chem. 2003;2003(16):3153-3161;
23. Wang CD, Shi XZ, Xie RJ – Synthesis of diacetals of 2,2-bis(hydroxymethyl)-1,3-propanediol under microwave irradiation. Synth Commun. 17;27(14):2517-2520;
24. Grosu I, Mager S, Plé G, Horn P – Axial and helical chirality of some spiro-1,3-dioxanes. J Chem Soc, Chem Commun. 1995;1995:167-168;
25. Gâz ŞA, Condamine E, Bogdan N, Terec A, Bogdan E, Ramondenc Y, Grosu I – Synthesis and stereochemistry of some new spiro and polyspiro-1,3-dithiane derivatives. Tetraheron. 2008;64: 7295-7300;