Synthesis and structural studies of novel 1,3,4-oxadiazolophanes

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The title compounds have been prepared in moderate yields from compound 2a/b as starting unit, which are obtained, in good yields by one-step process in high purity. Interesting results have been obtained when the cyclisation products were studied for structural analysis. The title compounds are also studied for their use as PTC agents.

Since the discovery of crown ethers by Pedersen1, the chemistry of macrocyclic compounds has developed in a new dimension viz. cation complexation using the legating macrocycles and their applications to biological and physical sciences2. In the pursuit of obtaining macrocycles having maximum legating ability and applicability to the needs of modern scientific requirements, a large number of macrocycles have been synthesized and reported till-date3. The field of heterophanes where heteroaromatic subunits are incorporated in the macrocycles is no exception to this4.

In continuation of our work on the chemistry of heterophanes5, we now report the synthesis and structural studies of novel 1,3,4-oxadiazolophanes. The oxadiazole unit is well-known for its biological6 and optical properties7. Very few methods are known for the synthesis of 2,5-bis (2-hydroxyphenyl)-1,3,4-oxadiazole 2, the basic unit used for the construction of the title compounds. It was observed that none of the reported methods produced the desired product in good yield and the product required critical purification before further use. It was therefore thought to carry out self-condensation reaction of the salicylic acid hydrazide followed by dehydration in PPA. This reaction afforded 2 in good yield and high purity (Scheme I).

The dipotassium salt of 2a,b was then reacted with 1,α-dihaloalkanes in 80% aq. methanol under high dilution to obtain the desired heterophanes (Scheme II). GC-MS analysis of the crude product from reaction of potassium salt of 2a with 1,3-dibromopropane revealed that only one product 3a was formed in very high purity. Similar results were obtained with higher homologous 1,α-dihaloalkanes.

Our attempts to synthesize similar compounds with diiodomethane and 1,2-dibromoethane were unsuccessful under similar experimental conditions. This could be explained from the molecular modeling studies8. It was observed that the distance between the two phenolic groups in the synthon 2 was approx. 4Å, which far exceeded the distance between the ethereal oxygen and the second carbon atom of dibromomethane, which was approx. 2.54 Å (Figure 1). Since the distance is too large, the attack of phenoxide ion on the β-carbon atom of ethylene bearing bromine involves very high strain. In case of diiodomethane the attack appeared to be impossible. In 1,3-dibromopropane the distance between the two terminal carbon atoms was found to be compatible with the distance between the two phenoxide ions. With other higher alkanes the flexibility of alkyl chain allowed the rear attack of phenoxide ion on the terminal carbon atom affording the desired products.

Similarly, the reaction of 1,2-bis[bromomethyl]benzene afforded the desired heterophanes in good yield. It was observed that addition of PTC like 18-Crown-6 did not affect the yields of heterophanes.

Nomenclature: The naming systems for the heterophanes developed by Vögtle and Newmann9 has been accepted by IUPAC. The same was used to name the oxadiazolophanes synthesized. Thus, the names of compounds 3a and 3b (Figure 2) would be 1,5,16-trioxa-(2',5')-diphenyl-1',3',4'-oxadiazolo[5]
It was observed that the oxadiazoloophanes were soluble in alcoholic sodium hydroxide. It was thought to study the applications of these compounds as phase transfer catalysts (PTC). Synthesis of acetylenes involves elimination reactions, which are very sensitive and require precise control over the reaction conditions. Recently, Verkuijse reported the synthesis of 1-butylacetylene 7 which is a well-known pharmaceutical intermediate, from 1,1-dichloro-3,3-dimethylbutane 8 using Aliquate-336 as a PTC, high boiling petroleum solvent (BP > 170°C) and solid potassium hydroxide as base. In the synthesis of 7 from pinacolone 10 via intermediate dichloride 9, similar results were obtained when compounds 4a and 6a were used as PTC (Scheme III).
Experimental Section

Melting points were taken in open capillaries and are uncorrected. NMR spectra were recorded on Varian-300 and Bruker-AMX-500 spectrometer using CDCl₃ as solvent. GC-MS spectra were recorded on Hewlett Packard 5989B, instrument using CHCl₃ as solvent (0.7 mL/min) and El (70eV) method.

General Procedure for the synthesis of 2,5-bis-(2-hydroxyphenyl)-1,3,4-oxadiazoles 2a/2b. 0.01 Mole of salicylic acid hydrazide was added to freshly prepared aq. potassium hydroxide and recrystallised from dilute aq. methanol up to half volume and allowed to cool. A solid compound separated out which was repeatedly washed with aq. DMF. 2.324(p, 2H, J=5Hz, -O-CH₂), 2.41(s, 6H, -CH₃), 4.21 (t, 4H, J=5Hz, O-CH₂-C), 6.936-8.160(m,8H,Ar-H); ¹³C NMR: δ 15.10(-CH₃), 31.33(-O-C-C-), 68.59(O-C-C), 107.01, 119.6, 124.22, 126.98, 134.93, 155.96 (Ar-C), 163.11ppm (C=N).

1, 6, 17-Trioxa-(2',5')-diphenyl-1',3',4'-oxadiazolo[6]phane 4a: Yield 35%, m.p.185°C, ¹HNMR: δ 2.139(m, 4H, -O-(CH₂)₂-C-O), 4.149(m,4H,2x-O-(CH₂)₂-C), 6.988-8.264(m, 8H, aromatic); ¹³C NMR: δ 26.428(O-(C-(CH₂)₂-C-O), 69.566 (2x-O-CH₂), 113.691, 120.916, 129.698, 132.910, 157.372 (aromatic C), 163.846ppm (C=N). GC-MS: retention time 13.2min; Mass: m/z M⁺ 308(13.3%), 307(72.2%), 253(21.1%), 121(100%), 105(13.3%), 92(38.8%), 64(24.4%).

General Procedure for the synthesis of oxadiazolophanes 3a-6b. Containing 1,7,18-Trioxa-(2',5')-diphenyl-1',3',4'-oxadiazolo[7]phane 5a: Yield 28%, m.p.95°C, ¹HNMR: δ 1.884-1.947(m, 6H, O-(CH₂)₂-C(CH₂)₂-C-O), 4.197(t, 4H, J=5MHz, 2x-O-CH₂), 7.625-8.111(m,6H,Ar-H); ¹³C NMR:δ 20.495 (O-CH₂), 26.685 (2x-O-CH₂), 66.632 (2x-O-CH₂), 112.687, 113.882, 120.669, 131.269, 132.800, 156.941 (aromatic C), 164.786ppm (C=N).
(s,4H-CH=2), 7.234-8.219 (m, 10H, Ar-H); 13C NMR: 16.513 (-CH3), 74.969 (-OCH3-), 118.196, 124.900, 127.974, 129.146, 132.086, 133.309, 135.056, 136.305, 155.244 (aromatic C), 164.068 ppm (C=N).

**Synthesis of pinacolone dichloride 10 form pinacolone.** High boiling petroleum solvent (BP > 170°C, 50 mL) was taken in a three-necked RB flask equipped with a mechanical stirrer and water condenser. 57.5g of PCl3 was added to it and the contents were stirred for 10 min. The reaction mass was cooled to 0°C and 25g pinacolone was added to it over a period of 2hr while maintaining the temperature below 5°C. After addition was complete the mixture was stirred for 9hr at room temperature (28-30°C). It was then poured in cold water maintaining temperature at 30°C. The petroleum layer was separated and washed with aq. sodium bicarbonate followed by cold water. It was then dried over calcium chloride and directly used for further synthesis of compound 8.

**Synthesis of t-butylacetylene 8.** Pinacolone dichloride 10 in petroleum ether was taken in a three-necked RB flask equipped with a mechanical stirrer and condenser with cold-water circulation. 0.01g Catalyst (4a and 6a) and 15g of sodium methoxide in 10 mL DMSO was added to it with stirring over a period of 2hr maintaining temperature below 30°C. After complete addition, the mixture was stirred for further 2hr while maintaining temperature at 30°C. On fractional distillation the fractions of the distillate at 40°C were collected in an externally cooled flask. On redistilling the contents compound 8 was obtained in 65% yield. Formation of compound 8 was confirmed by comparing its GC with an authentic sample obtained from Merck.

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**References and Notes**

11. Molecular modeling was carried out on Silicon Graphics IRIS Indigo computer using the Insight II and Discover software from MSI, USA. Models were built with the Builder module in Insight II. Energy of the molecules was calculated using CVFF force fields and minimized with a combination of Steepest Descents, Conjugate gradients and Newton Raphson techniques available in Discover. Ref. Discover User Guide, Version 2.9.5, MSI, 1993.