Iranian Journal of Organic Chemistry Vol. 3, No. 3 (2011) 675-679

Synthesis and characterization of two new macroheterocycles prepared from the reaction of 2,6-bis (chloromethyl) pyridine and thiodiglycol

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Received: June 2011; Revised: June 2011; Accepted: July 2011

Abstract: Two pyridine containing macroheterocycles have been synthesized from the reaction of 2,6-bis (chloromethyl) pyridine and thiodiglycol (TDG) in THF using NaH as base. Column chromatography was applied to the reaction mixture and two different macroheterocycles obtained were characterized by ^{1}H and ^{13}C-NMR as well as MS spectroscopy. The results confirm that [1+1] and [2+2] macroheterocycles are formed during cyclization reaction.

Keywords: Macroheterocycle, 2,6-bis (chloromethyl) pyridine, Thiodiglycol.

Introduction

Different pyridine aza crown ethers containing 2,6-pyridine moiety have already been introduced in the literatures among which three classes are more extensively studied [1-8]. In the first class, the pyridine unit is directly attached to heteroatom such as O, S and N [1]. The second class is built up from pyridine-2,6-diester moieties connected, through bridging -CH_2CH_2O-, to each other [2,3]. In the third class which is the subject of this study, the macroheterocycle involves 2,6-pyridinedimethylene subunits connected through –CH_2CH_2X- segments [4-8].

In this work, the synthesis of pyridinoazacrownethers [1+1] and [2+2] (Scheme **1**) by a single reaction of 2,6-bis(chloromethyl)pyridine and thiodiglycol (TDG) are reported. These two macroheterocycles were separated by column chromatography, then, characterized by NMR and MS spectroscopy.

Results and discussion

Preparation of 2,6-bis (chloromethyl) pyridine from pyridine2,6-dicarboxylic acid, as starting compound, was first performed using thionyl chloride as chlorinating reagent (Scheme **2**).

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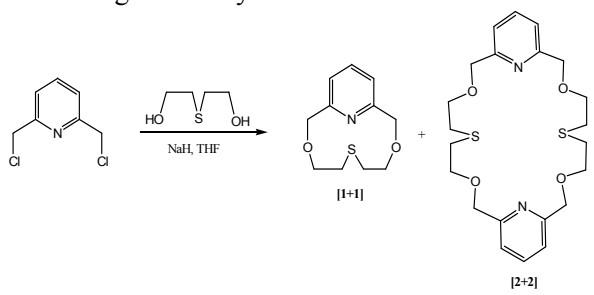
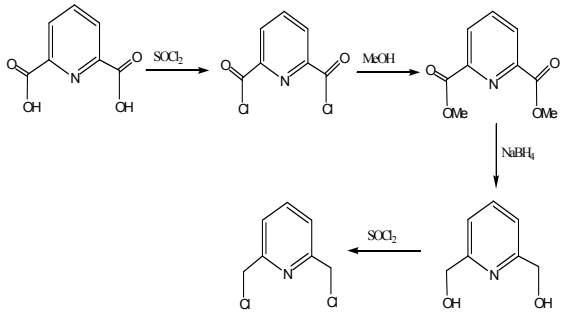
Esterification reaction on the resulting acid chloride by CH_3OH was applied to reach dimethyl 2,6-pyridine dicarboxylate. Pyridine dimethylester was reduced by $NaBH_4$ to get the corresponding alcohol 2,6-bis (hydroxymethyl) pyridine, followed by the alcohol-alkyl halide transformation to obtain 2,6-bis (chloromethyl) pyridine in an overall yield of 52.5% from starting dicarboxylic acid.



Scheme 1. Synthesis of Macroheterocycles [1+1] and [2+2] by the reaction of 2,6-bis(chloromethyl)pyridine and TDG in the presence of NaH as base.

The cyclization reaction was carried out in THF at reflux for 23h. Column chromatography was applied to the reaction mixture to purify the resulting macrocycles using EtOAc/n-Heptane as an eluent. 41 fractions were collected and analysed by TLC. The

results indicated the presence of two products in the reaction mixture.



Scheme 2. preparation of 2,6-bis (chloromethyl) pyridine from pyridine 2,6-dicarboxylic acid as starting compound.

The first 13-16 fractions were combined and the solvent evaporated and the residue was analysed by ^{1}H-NMR, ^{13}C-NMR and MS spectroscopy. On the basis of the ^{1}H-NMR spectrum there should be just one pyridine ring in the structure of the compound isolated from the 13-16 fractions (Fig. **1**) because of the existence of a single triplet for the pyridine H4 at 7.7 ppm. Three possible pyridine containing compounds I, II and macrocycle [1+1] as shown in Fig. **2**, were considered as appropriated candidate.

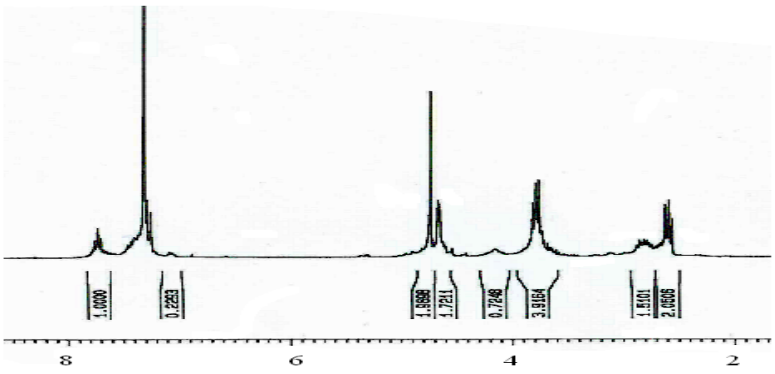


Fig. 1. ^{1}H-NMR spectrum of the sample obtained from the fractions 13-16 obtained from column chromatography.

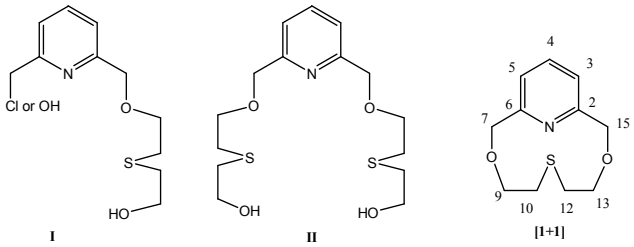


Fig. 2. Three possible structures proposed for the compound obtained from fractions 13-16.

The proposed structure II was rejected because of the aliphatic to aromatic hydrogen peak ratio obtained by integration in ^{1}H-NMR that has been 12:3. This was further tested by ^{13}C-NMR (Fig. **3**), which didn't show any peaks at δ=61ppm, related to CH_2OH group. The ^{13}C-NMR spectrum indicated mainly six different carbon atoms, in agreement with macrocycle [1+1], whereas the two other proposed structures need more than six peaks.

It is noted that a precise analysis on the number of ^{1}H peaks of aliphatic hydrogens in ^{1}H-NMR indicates that the four methylene hydrogens at 7 and 15 positions as well as those of CH_2S hydrogens have been individually divided into two chemically nonequivalent groups. The four hydrogen atoms attached to C7 and C15 have been appeared as two singlets at 4.6 and 4.8 ppm while

those of CH_2S at two different multipletes at 2.5 and 2.8 ppm. Interesting, in the ^{13}C-NMR spectrum (Fig. **3**) just one single resonance has been shown for each of the C7 and C15 as well as C10 and C12 couples, indicating the chemically equivalent carbon atoms. This could be due to the conformational parameter as a result of the orientation of S atom that reduces the molecular symmetry. To testify such proposal, structural analysis was performed using ChemOffice software. The solved structure has been shown in Fig. **4**. As is clear, the S atom has been backwarded to the 12-membered ring, imposing nonequivalency to the every methylene hydrogen atoms.

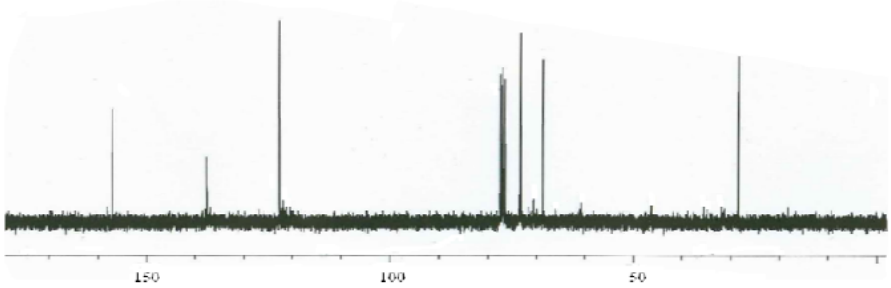


Fig. 3. The ^{13}C-NMR spectrum of the compound obtained from the fractions 13-16.

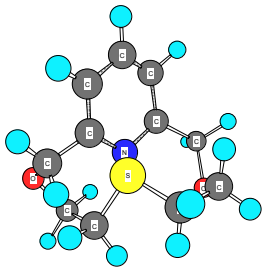


Fig. 4. 3D structure for [1+1] macroheterocycle optimized by ChemOffice.

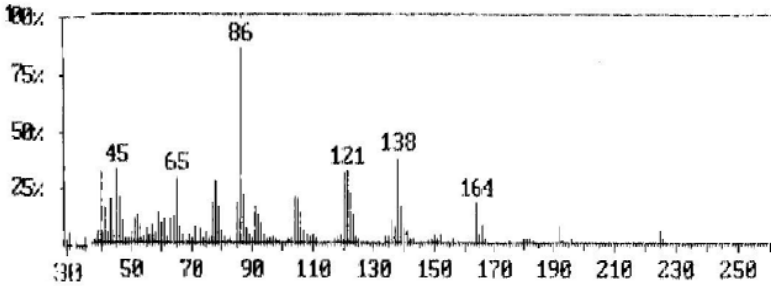


Fig. 5. The MS spectrum of the compound obtained from the fractions 13-16.

The structural analysis was also performed by MS spectrum to confirm **macroheterocycle [1+1]** (Fig. **5**). In the MS spectrum, the molecular ion mass at m/z=226 confirmed the macrocycle [1+1]. The main peaks in MS spectrum, m/z 86, 121, 138 and 165 could be related to fragments a-d respectively (Fig. **6**).

Fractions 31-39 containing the second main product were combined and the solvent was evaporated. The resulting residue was analysed by NMR and MS spectroscopy. The ^{1}H-NMR spectrum of this sample was more or less similar to that of the first fraction, the macrocycle [1+1]. It indicated the expected peaks for pyridine ring. Also, two multiplete peaks for CH_2O and CH_2S hydrogens with the same integration was obvious while the hydrogen atoms of the methylene group attached to the pyridine ring has given two singlets very close in chemical shifts. The similarities between the ^{1}H-NMR spectra of the current sample and that of the [1+1] macroheterocycle was an indication

of the possibility of the existence of [2+2] macroheterocycle as the second isolated product.

The ^{13}C-NMR spectrum revealed a very similar spectrum with minor changes on the chemical shifts. Three peaks in the aromatic region at 120.2 (meta carbon), 137.2 (para carbon) and 157.5 (orto carbon) and three aliphatic peaks for CH_2 carbons at 32.1(CH_2S), 70.9(CH_2O), 73.4(CH_2) were all indicative of the [2+2] macroheterocycle.

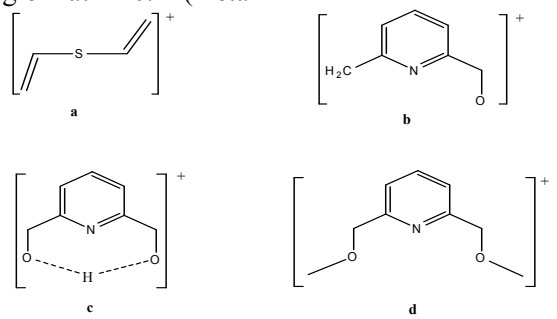


Fig. 6. The proposed fragments a-d observed in the MS spectrum of the compound obtained from the fractions 13-16.

The MS spectrum (Fig. **7**) confirmed that this compound must be macroheterocycle [2+2] not only because of the molecular ion peak at m/z=450 but also the similarity between the fragmentation observed in the current MS spectrum to that of [1+1] macroheterocycle.

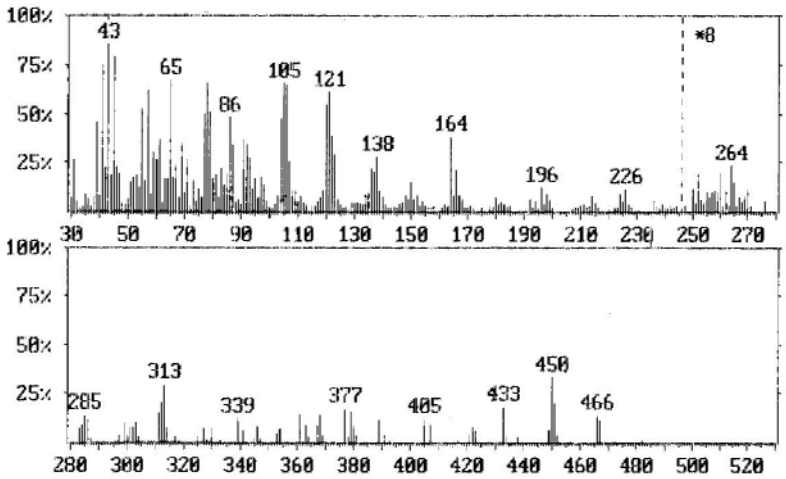


Fig. 7. The MS spectrum of fractions 31-39 containing macroheterocycle [2+2] as main product.

Experimental

General procedure:

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 250 and 62.5 MHz respectively on Bruker spectrometer. The GC-MS spectra were recorded on a Shimadzu spectrometer. All chemical shifts reported are relative to tetramethylsilane. The melting points were recorded on Electrothermal 9100. Chemoffice software package was applied to optimize 3D structure of macroheterocycle [1+1]. TDG was prepared by Dr. Moghimi et al., NaH was purchased from Aldrich Company, and solvents were purchased from Merck Company.

*Preparation of 2,6-bis(chloromethyl)pyridine (Scheme **2**):*

A solution of 16.7g (100mmol) of 2,6-pyridinedicarboxylic acid in 100ml of thionyl chloride was heated at reflux for 21h. Thionyl chloride was distilled, and the residue was cooled in an ice bath to yield 19.4g (95%) pyridine 2,6-dicarbonyl chloride as needle crystals, m.p. 59-60^{o}C. 10.2g of pyridine 2,6-dicarbonyl chloride was dissolved in 60ml methanol and heated at reflux for 1h, then the excess of methanol was distilled. The solution was cooled in an ice bath, and the dimethyl 2,6-pyridine dicarboxylate which formed was filtered and washed with cold (0^{o}C) methanol to yield 9.1g (93%) of the diester, m.p. 118-

121°C. A suspension of 8.78g (45mmol) of the above diester in 60ml methanol was stirred and cooled in an ice bath as 5.67g (150mmol) of sodium borohydride was added in portions over 20 min. The mixture was stirred at 0°C for 1h. The ice bath was removed, and an exothermic reaction warmed the mixture to reflux. The mixture was stirred at RT for 3h, after which it was heated at reflux on a steam bath for 10h. The solvent was distilled in vacuo, the residue was mixed with 40ml of acetone and was heated on a steam bath for 1h and the solvent was distilled in vacuo. The residue was dissolved in water. The aqueous solution was extracted continuously with $CHCl_3$ for 4 days, to give 5.6g (90%) of 2,6-bis (hydroxymethyl) pyridine, m.p. 112-115°C [5].

70 ml of thionyl chloride was slowly added to 5.5g of 2,6-bis(hydroxymethyl) pyridine in 100ml flask at 0°C, and the mixture was warmed on a water bath for 5h, then cooled and treated with 100ml of benzene. The precipitated hydrochloride was collected, washed with benzene, dried, dissolved in water and neutralized with sodium carbonate. The 2,6-bis(chloromethyl)pyridine was collected and crystallized from 100ml n-Heptane as needles (4.2g), m.p. 76-79°C, ^{1}H-NMR ($CDCl_3$, δppm) 4.65(s, 4H), 7.4(d, 2H), 7.73(t, 1H), ^{13}C-NMR ($CDCl_3$, δppm) 46.5, 122.1, 138.1, 156.3 [9].

Synthesis of macroheterocycle [1+1] and [2+2]:

0.44g (11mmol) of sodium hydride (60% in oil) suspended in 15ml THF was added to 0.52ml (5mmol) of TDG dissolved in 35ml THF, and heated to reflux for 1.5h. The mixture was cooled and a solution of 0.88g (5mmol) of 2,6-bis (chloromethyl) pyridine dissolved in 50ml THF was slowly added to it. The mixture was stirred at room temperature for 2h, and heated to reflux for 23h, then cooled and filtered. The solution phase was concentrated and purified by column chromatography using silica gel with CH_3COOEt/n-heptane as eluent, fractions 13-16 were added together and evaporated to give macroheterocycle [1+1] as yellow oil. ^{1}H-NMR ($CDCl_3$, δppm) 2.5(m, 2H, CH_2S), 2.8(m, 2H, CH_2S), 3.7(m, 4H, CH_2O), 4.6(s, 2H, CH_2), 4.8(s, 2H, CH_2), 7.3(d, 2H), 7.7(t, 1H), ^{13}C-NMR($CDCl_3$, δppm) 28.5(CH_2S), 68.6(CH_2O), 73.2(CH_2), 121(meta carbon), 137.5(para carbon), 156.9(ortho carbon), MS: m/e 225(M^+), 192, 164, 138, 121, 104, 86(main peak), 45

Fractions 31-39 were mixed together, evaporated to give macroheterocycle [2+2]. ^{1}H-NMR ($CDCl_3$, δppm) 2.8(m, 8H, CH2S), 3.7(m, 8H, CH_2O), 4.5(s, 4H, CH_2), 4.6(s, 4H, CH_2), 7.3(m, 4H, meta hydrogen), 7.5(t, 1H, para hydrogen), 7.7(t, 1H, para hydrogen), ^{13}C-NMR($CDCl_3$, δppm) 32.1(CH_2S), 70.9(CH_2O), 73.4(CH_2), 120.2(meta carbon), 137.2(para carbon), 157.5(orto carbon), MS: m/e 450(M^+), 313, 264, 226, 164, 121, 105, 86, 65, 43(main peak).

Acknowledgements

We gratefully acknowledge the support of this work by the Imam Hossein University (IHU).

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