



Synthesis of some new 1,2,4-triazole derivatives

F. Lazrak*^{1,2}, A. Keita², Y. Ramli¹, K. Karrouchi¹, Y. Zaoui¹, M. Ansar¹, J. Taoufik¹
and E. M. Essassi²

¹Medicinal Chemistry Laboratory, Faculty of Medicine and Pharmacy, Rabat Institute,
Mohammed V University-Rabat, Morocco

²Laboratoire de Chimie Organique Hétérocyclique URAC 21, Pôle de Compétences
Pharmacochimie, Av. Ibn Battouta, BP 1014, Faculté des Sciences,
Université Mohammed V, Rabat, Morocco

ABSTRACT

We describe herein the synthesis of new macrocycles and podants derived from the 3-alkyl (phenyl)-1,2,4-triazole-5-thiones 1a-c in a heterogeneous media using phase transfer catalysis. The compounds were characterized using ¹H NMR, ¹³C-NMR and Mass Spectral.

Keywords: Triazole, Dihalogeno (di)triethylene glycol, Phase transfer catalysis.

INTRODUCTION

Heterocyclic systems containing 1,2,4 -triazole aroused great interest by researchers [1-3] because of their applications in important areas as diverse as pharmacology, agriculture, industry. The 1,2,4-triazoles and certain of its derivatives are known for their anti-inflammatory properties [4,5], as analgesics [6,7], diuretics [8], bronchodilators [9], anticancer [10], antioxidant [11] and antimicrobial [12,13]. The use of certain 1,2,4-triazole derivatives in the industry conferred greater stability and heat resistance in many molecular materials [14] and highlighted the corrosion inhibiting properties of certain metals [15]. In agriculture, 1,2,4-triazoles are deemed to be fungicides [16,17], bactericides [18] and herbicides [19].

Moreover, the main feature of polyester and cyclic nitrogen or sulfur derivatives lies in their ability to form stable complexes with cations [20,21], thus can be applied in various chemical and biochemical fields; namely: recognizing [22], processing more reactive anions accompanying the cation as a base and separating the ion pairs [23]. In biology, they are used for determining the concentration of sodium and potassium in the blood and in other biological fluids [24]. In physiology, they are used for ions transfer across cell membranes or artificial [25].

The importance of these products has encouraged us to continue our research in this area. Thus, in this work we report new methods for synthesizing heterocyclic system oxygen and sulfur derivatives of 1,2,4-triazole and 1,1-bis (5-mercapto-3-alkyl (phenyl) -1,2,4-triazolyl) methanes. The synthesis of the compounds was illustrated in Scheme 1, 2, 3 and 4.

EXPERIMENTAL SECTION

Melting points were determined on Electrothermal apparatus and are not corrected. ¹H and ¹³C NMR spectra were recorded on an AC 250 MHz and 400 MHz Bruker device. The chemical shifts (δ) are given in ppm relative to

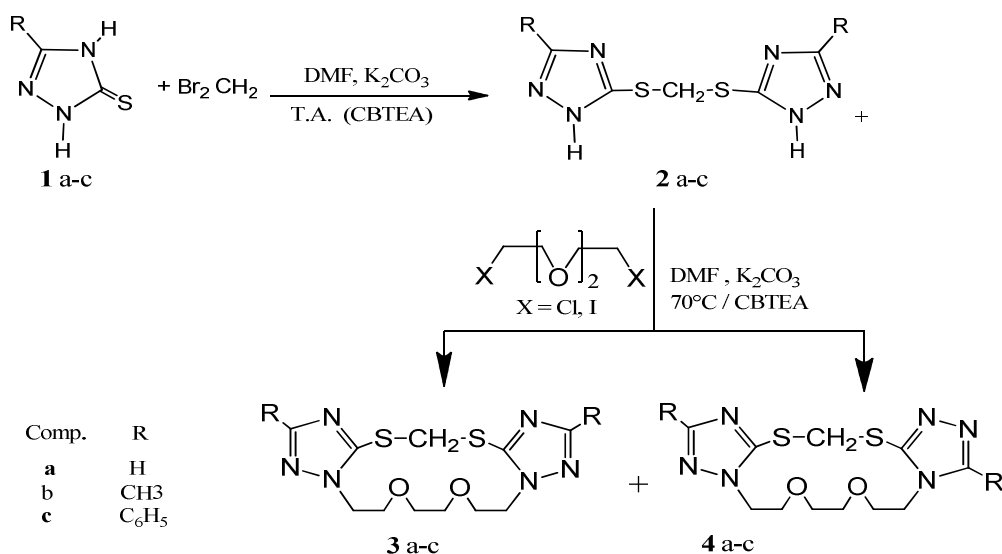
tetramethylsilane (TMS) taken as internal standard. Mass spectra was recorded on a Perkin Elmer Sciex API 100 and Varian MAT 311A (Paul Sabatier University in Toulouse).

RESULTS AND DISCUSSION

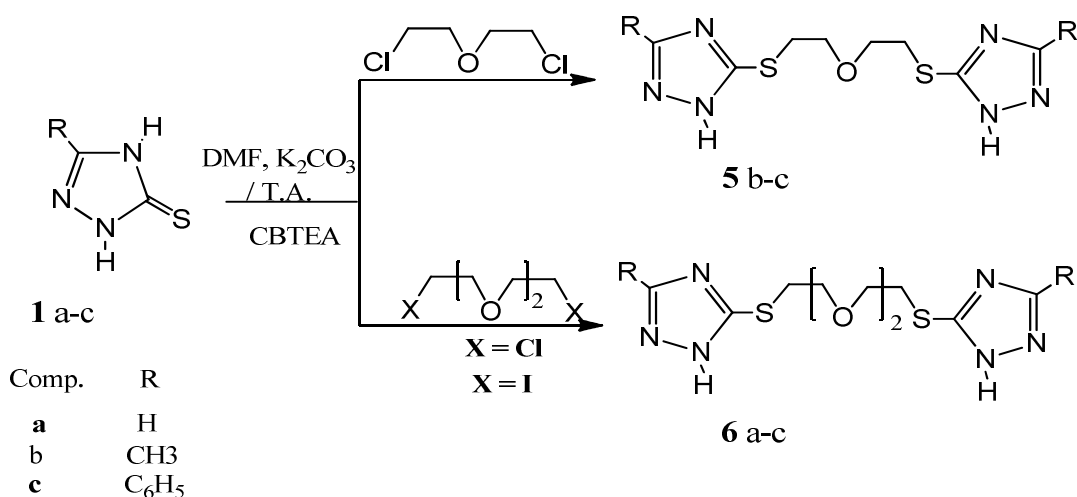
Synthesis of dialkyl(diphényl)-dithiazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6: 3a-c – 4a-c :

To a solution of alkyl-1,2,4-triazole-5-thione (0,008 mole) **1a-c** and dibromomethane (0,004 mol) in dimethylformamide (60 ml), potassium carbonate (0,016 mol) and (0,0008 mole) of the benzyltriethyl ammonium chloride BTEAC (catalyst) were added. The mixture was stirred at room temperature for 24hr. The solution was filtered and the filtrate was evaporated. The residue was recrystallized from ethanol to give product **2a**, **2b** or chromatographed over silica gel using a mixture of (hexane/ethyl acetate: 70/30) as eluant to give **2c**.

Then to a solution of 1,1-bis(5-mercapto-3-alkyl(phenyl)-1,2,4-triazolyl) methane (0,008 mole) **2a-c** and dichlorotriethylene glycol (0,008 mole), potassium carbonate (0,016 mol) and (0,0008 mole) of the benzyltriethyl ammonium chloride BTEAC (catalyst) were added. The mixture was stirred for 24h at 303K, then filtered and dried. The crude material was chromatographed over alumina gel using a mixture of (hexane/ethyl acetate: 70/30) as eluant to give **3a**, **3c**, **4a**, **4c** or silica gel using a mixture of (hexane/ethyl acetate: 60/40) as eluant to give **3b**, **4b**.



Scheme 1: Synthèse des dialkyl(diphényl)-dithiazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6: 3a-c – 4a-c



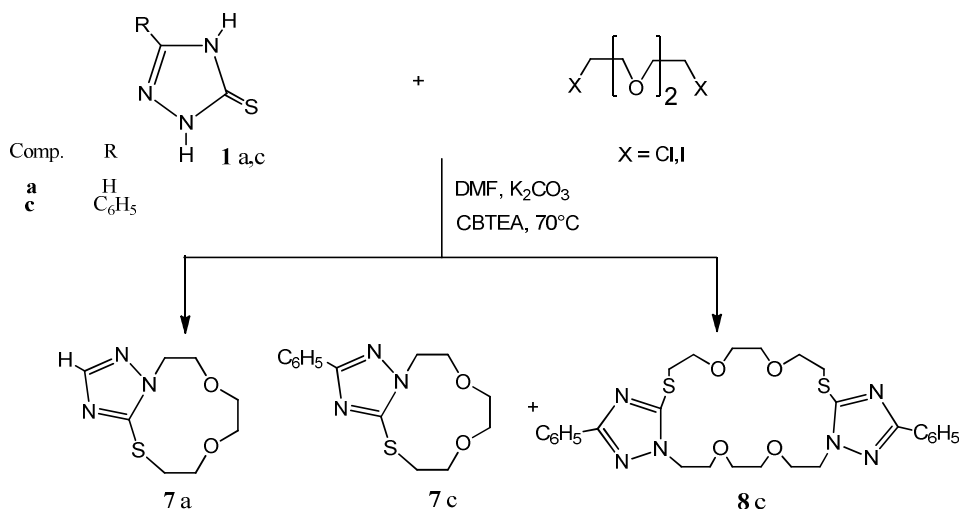
Scheme 2: Synthesis of 1,5-bis(5-mercapto-3-méthyl(phényl)-1,2,4-triazolyl) diéthylenglycol et du 1,8-bis(5-mercapto-3-alkyl(phenyl)-1,2,4-triazolyl) triéthylenglycol : 5b-c, 6a-c

Synthesis of 1,5-bis(5-mercapto-3-méthyl(phényl)-1,2,4-triazolyl) diéthylèneglycol et du 1,8-bis(5-mercapto-3-alkyl(phényl)-1,2,4-triazolyl) triéthylèneglycol : 5b-c, 6a-c :

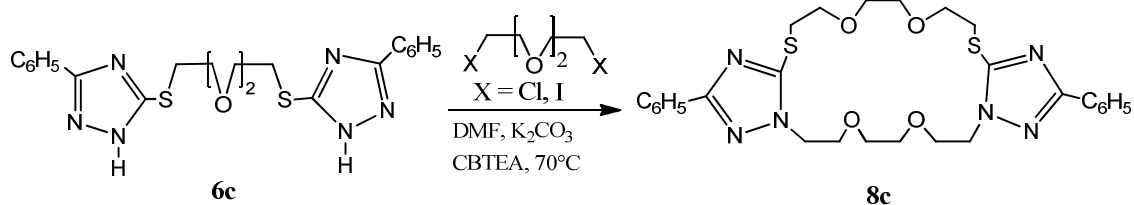
To a solution of thioure (0,008 mole) **1a-c** and dihalogenodiéthylèneglycol or dihalogenotriéthylene glycol (0,004 mole), in dimethylformamide (40 ml), potassium carbonate (0,016 mol) and (0,0008 mole) of the benzyltriethyl ammonium chloride BTEAC (catalyst) were added. The mixture was stirred at room temperature for 24hr. The solution was filtered, the filtrate was evaporated. The residue was chromatographed over silica gel using a mixture of (ethyl acetate) as eluant to give **5b, 6a, 6b** and (hexane/ethyl acetate: 70/30) as eluant to give **5c, 6c**

Synthesis of 1,2,4-triazolo[2,3-h]-7,9-thiaza-11-couonne-4 : 7a, 3-phényl-1,2,4-triazolo[2,3-h]-7,9-thiaza-11-crown-4 : 7c, 17-dithia-8,15-diaza-bis[3-phényl -1,2,4-triazolo][3,2-e][2,3-o]- crown -8 : 8c

To a solution of 1,2,4 - triazole-5-thione (1.01 g, 0.01 mol) and dichlorotriéthylene glycol (1.87 g, 0.01 mol) in dimethylformamide (60 ml) , potassium carbonate (4.15 g, 0.03 mol) were added. The mixture was stirred for 24h at 303K, then filtered and dried. The residue was extracted by chromatography over silica gel or alumina gel, using (ethyl acetate) as eluant to give **7a**, (hexane/ ethyl acetate: 75/25) as eluant to give **7c** and **8c**



Scheme 3: Synthesis of 1,2,4-triazolo[2,3-h]-7,9-thiaza-11-crown-4 : 7a, 3-phényl-1,2,4-triazolo[2,3-h]-7,9-thiaza-11-crown-4 : 7c, 17-dithia-8,15-diaza-bis[3-phényl -1,2,4-triazolo][3,2-e][2,3-o]- crown -8 : 8c



Scheme 4: Synthesis of 17-dithia-8,15-diaza-bis[3-phényl -1,2,4-triazolo][3,2-e][2,3-o]- crown -8 : 8c

The data of physical characteristics and the spectral data (^1H NMR, ^{13}C -NMR and Masse Spectra) of synthesized compounds are listed below.

1,1-bis(5-mercapto-3-H-1,2,4-triazolyl)methane (2a)

Yield 50%(solid); M.p. 120-121°C; ^1H - NMR (250 MHz, d_6 -DMSO, δ (ppm)): δ = 4.85 (2H, S-CH₂S), 8.49 (2H, CH Triazole); ^{13}C -NMR(400 MHz, d_6 -DMSO, δ (ppm)): δ = 34.64 (S-CH₂), 146.11 (C3-H), 156.12 (C5 triazole).

1,1-bis(5-mercapto-3-méthyl-1,2,4-triazolyl)methane (2b)

Yield 82%(solid); M.p. 243-244°C; ^1H - NMR (250 MHz, d_6 -DMSO, δ (ppm)): δ = 4.73(2H, S-CH₂-S), 2.31(6H, CH₃); ^{13}C -NMR(400 MHz, d_6 -DMSO, δ (ppm)): δ = 32.25 (S-CH₂), 11.79 (CH₃), 154.59 (C3-CH₃), 156.82 (C5-triazole).

1,1-bis(5-mercapto-3-phényl-1,2,4-triazolyl)methane (2c)

Yield 60%(solid); M.p. 200-201°C; ^1H - NMR (250 MHz, d_6 -DMSO, δ (ppm)): δ = 5.04(2H, S-CH₂-S), 7.48-8.16(10H, Ar-CH); ^{13}C -NMR(400 MHz, d_6 -DMSO, δ (ppm)): δ = 35.17 (S-CH₂), 125.93 , 128.88 , 129.50 (Ar-CH).

2,15-H-ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (3a)

Yield 30%(solid); M.p. (huile); ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 5.05(2H, S-CH₂-S), 4.17 (4H, N-CH₂), 3.83(4H, CH₂-O), 3.57(4H, OCH₂), 7.83(2H, C-H Triazole).

2,15-dimethyl ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (3b)

Yield 45%(solid); M.p. 188-189°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 5.00 (2H, S-CH₂-S), 4.08(4H, N-CH₂), 4.02(4H, CH₂-O), 3.51(4H, OCH₂), 2.36(6H CH₃); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 14.22 (CH₃), 38.92 (CH₂-S), 48.05 (CH₂-N), 69.25 ,70.58 (CH₂-), 151.22, 161.34 (Cq).

2,15-diphenyl ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (3c)

Yield 70%(solid); M.p. 156-157°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 5.21 (2H, S-CH₂-S), 4.17(4H, N-CH₂), 3.85(4H, CH₂-O), 3.45(4H, OCH₂) , 7.23-8.15 (10H, Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 39.51 (CH₂-S) ,48.47 (CH₂-N) , 69.36 , 70.61 (CH₂-O), 126.33, 128.59, 129.34 (Ar-CH) ; 130.94 , 152.19, 162.46 (Cq); MS: m/z = 481 [M+H]⁺.

3,15-H- ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (4a)

Yield 10%(solid); M.p. (huile); ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.77 (2H, S-CH₂-S), 4.13-4.21 (4H, N1-CH₂, N4-CH₂), 3.60-3.76 (4H, O-CH₂CH₂N1, O-CH₂CH₂N4) 3.44 (4H, O-CH₂), 7.86 (1H, C–H Triazole) 7.93(1H, C–H Triazole); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 36.56 (CH₂-S), 48.78, 50.08 (CH₂-N), 68.19 , 68.73, 70.58 ,71.09 (CH₂-O), 149.40, 151.51 (CH triazole) , 158.20 ,159.99 (Cq).

3,15-dimethyl- ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (4b)

Yield 15%(solid); M.p. 140-141°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.70 (2H, S-CH₂-S), 4.06-4.15 (4H, N1-CH₂N4-CH₂), 3.56-3.98 (4H, O-CH₂CH₂N1, O-CH₂CH₂N4) , 3.50 (4H, O-CH₂), 2.34 (3H, CH₃), 2.36 (3H, CH₃); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 11.97 (CH₃), 14.07 (CH₃), 37.91 (CH₂-S) , 48.02, 48.67 (CH₂-N), 68.41, 68.86,70.47, 70.63 (CH₂-O), 150.39 , 154.52 ,156.13, 161.09 (Cq).

3,15-diphenyl- ditriazolo-1,3-dithia-8,11-dioxa-5,14-diaza-15-couronne-6 (4c)

Yield 20%(solid); M.p. 120-121°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.95 (2H, S-CH₂-S), 4.17-4.29 (4H, N1-CH₂,N4-CH₂), 3.68 (2H, O-CH₂CH₂N1, O-CH₂CH₂N4), 3.93 (2H, O-CH₂CH₂N1, O-CH₂CH₂N4); 3.56 (4H, O-CH₂), 7.35-8.05 (10H Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 38.45 (CH₂-S) , 48.52 , 49.44 (CH₂-N) , 68.35, 69.10 , 70.57, 70.93 (CH₂-O), 126.31, 128.50 , 128.75, 129.10 ,129.19, 130.24 (Ar-CH) , 127.43, 130.89, 151.29, 157.06, 157.16, 162.30 (Cq); MS: m/z = 481 [M+H]⁺.

1,5-bis(5-mercapto-3-methyl-1,2,4-triazolyl) diéthylèneglycol (5b)

Yield 50%(solid); M.p. 144-145°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 3.18 (4H, S-CH₂), 3.64 (4H, O-CH₂), 2.28 (6H, CH₃); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 30.25 (S-CH₂), 68.98 (O-CH₂), 11.52 (CH₃).

1,5-bis(5-mercapto-3-phenyl-1,2,4-triazolyl) diéthylèneglycol (5c)

Yield 68%(solid); M.p. 130-131°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 3.38 (4H, S-CH₂), 3.79 (4H, O-CH₂), 7.44-8.02 (10H, Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 30.91 (S-CH₂), 68.95 (O-CH₂), 125.87; 128.39; 132.67 (Ar-CH).

1,8-bis(5-mercapto-3-H-1,2,4-triazolyl) triéthylèneglycol (6a)

Yield 45%(solid); M.p. huile; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 3.21 (4H, S-CH₂), 3.66 (4H, O-CH₂), 3.53 (4H, O-CH₂-CH₂-O), 8.01(2H, C–H Triazole); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 31.33 (S-CH₂), 69.71 (O-CH₂), 69.80 (O-CH₂-CH₂-O),146.40 (C–H Triazole).

1,8-bis(5-mercapto-3-methyl-1,2,4-triazolyl) triéthylèneglycol (6b)

Yield 60%(solid); M.p. 122-123°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ 3.17 (4H, S-CH₂), 3.65 (4H, O-CH₂), 3.53 (4H, O-CH₂-CH₂-O), 2.29 (6H, CH₃); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 30.91 (S-CH₂), 69.63 (O-CH₂), 69.65 (O-CH₂-CH₂-O), 11.89 (CH₃); MS: m/z = 345 [M+H]⁺.

1,8-bis(5-mercapto-3-phenyl-1,2,4-triazolyl) triéthylèneglycol (6c)

Yield 75%(solid); M.p. 158-159°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 3.30 (4H, S-CH₂), 3.81 (4H, O-CH₂), 3.66 (4H, O-CH₂-CH₂-O), 7.33-8.01(10H, Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 32.51 (S-CH₂), 69.85 (O-CH₂), 70.59 (O-CH₂-CH₂-O) 126.42 ; 128.71;129.76 (Ar-CH).

1,2,4-triazolo[2,3-h]-7,9-thiaza-11-couronne-4 (7a)

Yield 70%(solid); M.p. 150°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.45 (2H, N-CH₂), 3.23(2H, S-CH₂), 3.60-3.65 (2H, CH₂-O), 3.96 (2H, CH₂-O) 3.53(4H, O-CH₂CH₂-O), 7.96(1H, C-H Triazole); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 37.19 (CH₂-S), 48.36 (CH₂-N), 68.94, 69.05, 69.23, 72.13 (CH₂-O), 151.32 (C5 triazole), 152.49 (C3 triazole); MS: m/z = 215.

3-phenyl-1,2,4-triazolo[2,3-h]-7,9-thiaza-11-couronne-4 (7c)

Yield 65%(solid); M.p. 115°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.43 (2H, N-CH₂), 3.22 (2H, S-CH₂), 3.54 (2H,CH₂-O) 3.97 (2H CH₂-O), 3.60 (4H, O-CH₂CH₂-O), 7.37-8.10 (5H, Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 37.49 (S-CH₂) , 48.39 (N-CH₂), 68.76, 69.12, 69.17, 72.19 (CH₂-O), 126.33, 128.57, 129.35 (CH Ar), 130.89 (Cq Ar), 151.84 (C5 triazole), 162.91 (C3 triazole); MS: m/z = 291.

4,17-dithia-8,15-diaza-bis[1,2,4-triazolo][3,2-e][2,3-o]-couronne-8 (8c)

Yield 15%(solid); M.p. 161°C; ¹H – NMR (250 MHz, d₆-DMSO, δ(ppm)): δ = 4.34 (4H, N-CH₂), 3.40 (4H, S-CH₂), 3.77-3.88 (8H, CH₂-O), 3.57 (8H, O-CH₂CH₂-O), 7.37-8.04 (10H, Ar-CH); ¹³C-NMR(400 MHz, d₆-DMSO, δ(ppm)): δ = 34.06 (S-CH₂), 49.00 (N-CH₂), 69.25, 69.95, 70.26, 71.10 (CH₂-O), 126.22, 128.57, 129.20 (CH Ar), 131.02 (Cq Ar) 153.40 (C5 triazole), 161.82 (C3 triazole); MS: m/z = 582.

RESULTS AND DISCUSSION

The alkylation reaction of compounds 1a-c with half equivalent of dibromomethane used in the conditions of phase transfer catalysis in dimethylformamide in the presence of potassium carbonate gives the 1,1-bis (5-mercapto-3 -alkyl (phenyl) -1,2,4-triazolyl) methane 2a-c. The action of dichlorotriethylene glycol was taken in stoichiometric amount of 2a-c in the same conditions at 70 ° C leads to a mixture of two isomers 3a-c major products and 4a-c minor products (scheme1).

The action of dihalo (di) triethylene glycol used in default on 1a-c, under the above conditions at room temperature. The reaction provided access to a single compound 5b-c and 6a-c in good yields (scheme2). Moreover, the action of a stoichiometric amount of glycol dichlorotriethylene 1a-c under the same conditions led to the isolation, after 24 hours of stirring at 70 ° C, of a single product type: 1,2,4-triazolo thiaza -11 7a-crown-4 when R = H. However, when R = C₆H₅, two compounds were isolated: one with 3-phenyl-1,2,4-triazolothiaza-11-crown-4 7c type, and the other with dithia tetraoxa diaza-22-crown-8 (8c) type (scheme3).

Note, secondly, that the 8c compound can be isolated by another synthetic route, by reacting a stoichiometric amount of equimolar dihalogeno triethylene on 1,8-bis (5-mercapto-3-phenyl-1, 2,4-triazolyl) triethylene 6c under the above conditions (scheme 4).

The isolated 7a, 7c, 8c compounds may have another structure involving the nitrogen atom at position 4 of the triazole cycle, the structures of compounds were established unambiguously by the results of the literature. Indeed, it has been shown that the sulfur atom is responsible for the first nucleophilic attack [26] against triethylene glycol and it is the reactivity of the nitrogens N1 or N4-H-H, which determines the structure of the isolated compound, this reactivity depends on the nature of the substituent at position 3 of the triazole nucleus [27], on the effect of the solvent [28] as well as the temperature of the reaction[29]. Furthermore, a cristalographique analysis with X-ray diffraction of compound 7a [30] shows that the cyclization reaction is regioselective and it occurs on the nitrogen N1 of the triazole cycle.

CONCLUSION

The Main focus of this research work was to synthesize, characterize of the newly synthesized 1,2,4-triazole-5thione derivatives. Structures of synthesized compounds were confirmed by means of their IR, ¹H NMR, ¹³C NMR and mass spectral.

These heterocyclic compounds may have different applications in important areas, from herbicides and fungicides to therapeutically usable drugs.

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