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**INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION OF  
DIAZIDO-TERMINAL DIALKYNES: SYNTHESIS OF NEW  
POLYOXYETHYLENE FUSED EXO-BIS(1,2,3-TRIAZOLO-  
1,4-OXAZINES)**

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**Abstract** – The synthesis of new tetraheterocyclic 1,5-disubstituted *exo*-heterocyclic polyoxyethylene bis(1,2,3-triazolo-1,4-oxazine) is achieved through nucleophilic azide ion ring opening reaction on polyoxyethylene dioxiranes, followed by an *O*-propargylation, then thermal uncatalyzed 1,3-dipolar intramolecular cycloaddition.

The polyheterocyclic compounds are widely found within natural substances such as steroids.<sup>1</sup> In particular the *N*-heterocyclic derivatives have found many applications.<sup>2</sup> The 1,2,3-triazoles are biologically active compounds, they are used in medicinal,<sup>3</sup> pharmaceutical,<sup>4</sup> agrochemical<sup>5</sup> and industrial fields.<sup>6</sup>

Oxazines constitute also an important class of heterocycles,<sup>7</sup> having a synthetic interest due to their large range of biological activities.<sup>8</sup> Several oxazine derivatives have various medicinal and pharmacological properties, such as anti-HIV drug.<sup>9-11</sup>

On the other hand, polyoxyethylene chains (p.o.e) are well described,<sup>12</sup> they are known for their biodegradability.<sup>13</sup> Polyoxyethylenes are used in different application fields,<sup>14</sup> such as pharmaceutical and medical adjuvants,<sup>15</sup> polymers<sup>16</sup> and tensioactive agents.<sup>17</sup>

In addition to their uses to modify physical properties of some molecules,<sup>18</sup> especially to increase their lipophilicity,<sup>19</sup> one of the interesting applications of the p.o.e. in chemistry is their use as spacers for different proposes<sup>20</sup> such as to separate functional group to each other,<sup>21</sup> to decrease the hindrance interactions, to obtain some functional groups so far from to each other<sup>22</sup> in order to make possible their reaction based on the important property related to their flexibility around the oxygen atoms.<sup>23</sup>

The (Cu<sup>+</sup> or Ru<sup>2+</sup>) catalyzed azide-alkyne cycloaddition is the best known of the 1,3-dipolar cycloaddition reaction.<sup>24,25</sup> It constitute actually the backbones reaction of the "Click Chemistry".<sup>26</sup> While the

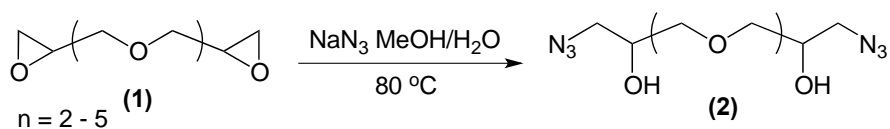
intramolecular cycloaddition presents a particular interest due to its potential use in the synthesis of polyheterocyclic systems,<sup>27</sup> it is very less described compared to the intermolecular one.<sup>28</sup> In the major cases the interest is focused on the target molecule rather than the mechanism, the structure and the development of the reaction.<sup>28, 29</sup>

Whereas the uncatalyzed intermolecular azide-terminal alkyne cycloaddition conduce generally to a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazolo isomers, the uncatalyzed intramolecular azido-alkyne cycloaddition conduce exclusively to the *exo*-cyclic 1,5-disubstituted isomer, especially in the case of five, six and seven membered heterocycles.<sup>30</sup> The 1,4-disubstituted 1,2,3-triazole (*endo*-cyclic) isomer cannot be produced due to the geometrical constraints and the low overlapping encountered.

Despite the great development of the intramolecular 1,3-dipolar azide-alkyne cycloaddition, only diazides were reacted with dialkynes or *mono* azido-alkynes.<sup>31</sup> But, to our knowledge basic reagents having both the two azide and two alkyne functional groups were not described. Until now the only diazido-dialkyne reported was described in our previous work and especially for the cycloaddition reactions.<sup>32</sup>

Herein we describe the synthesis of polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) via simple ring opening of the corresponding dioxiranes, followed by *O*-propargylation.

The polyoxyethylene diazido-diols (**2**) are obtained in good yields (Table 1) from the nucleophilic ring opening azide ion action on polyoxyethylene diepoxides (**1**) (Scheme 1).



**Scheme 1.** Synthesis of polyoxyethylene diazido-diols (**2**)

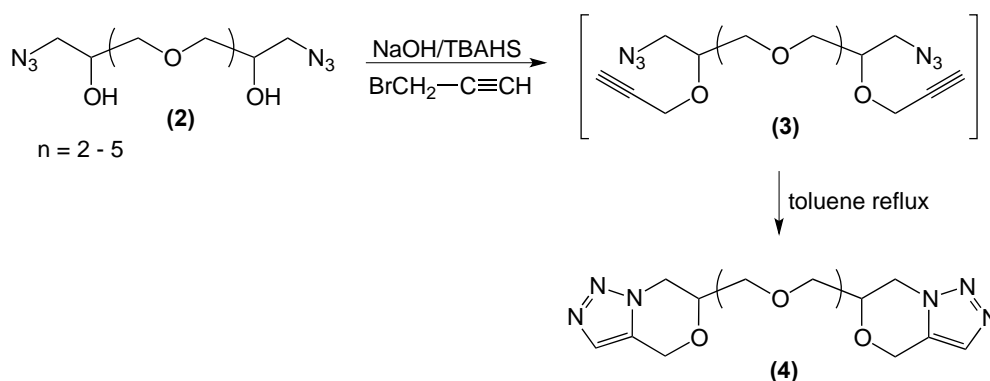
**Table 1.** Synthesized polyoxyethylene diazido-diols (**2**)

Entry	diazido-diols ( <b>2</b> )	Y (%)
1	<b>(2a)</b>	80
2	<b>(2b)</b>	83
3	<b>(2c)</b>	86
4	<b>(2d)</b>	91

The *O*-propargylation of the polyoxyethylene diazido-diols (**2**) is achieved by condensation with propargyl bromide in basic medium using of a phase transfer catalyst,<sup>33</sup> giving rise to the corresponding unstable polyoxyethylene di(azido-alkynes) (**3**) (Scheme 2). Compounds (**3**) decompose on their contact with air oxygen. So, they are not isolated but diluted in toluene to avoid their contact with air.

The synthesized diazido-dialkynes (**3**), can undergo different types of chemical reactions, such as the free radical and ionic additions, inter and intramolecular cycloadditions, oxidation, reduction reactions, etc.

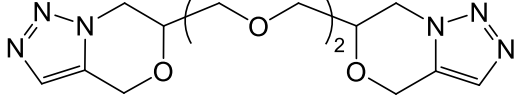
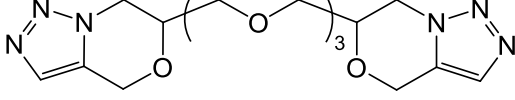
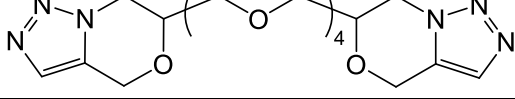
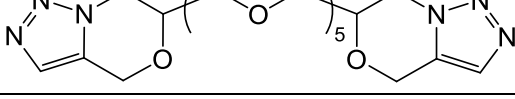
As a direct application, compounds (**3**) were heated in the same solvent, without catalyst. An intramolecular 1,3-dipolar cycloaddition occurs, yielding exclusively the stable 1,5-disubstituted *exo*-tetraheterocyclic polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**) (Scheme 2).



**Scheme 2.** Synthesis of polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**)

The cyclization reaction of compounds (**3**) is spontaneously possible at room temperature, but it is relatively slow. For this reason, the polyoxyethylene di(azido-alkynes) (**3**) were heated at reflux in toluene yielding exclusively compounds (**4**) (Table 2). The two reaction side groups are so remote from each other that they react as two independent molecules.

**Table 2.** Synthesized polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**)

Entry	Polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) ( <b>4</b> )	Y (%)
5	 <b>(4a)</b>	83
6	 <b>(4b)</b>	83
7	 <b>(4c)</b>	85
8	 <b>(4d)</b>	88

Compounds (**2** and **4**) were identified by IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopies, as well as by HRMS and elementary analysis. On the  $^1\text{H}$  NMR spectrum of compounds (**4**), the two allylic protons  $\text{O-CH}_2\text{-C=}$  constitute an *AB* system resonating at  $\sim 5$  ppm, ( $^2J_{AB} \sim 15$  Hz). Two other protons  $\text{CH}_2\text{-N}$  are also non equivalent and constitute the *AB* part of an *ABX* system ( $^2J_{AB} \sim 12$  Hz), with the proton of the asymmetric carbon atom  $\text{HC}^*$ , constitute the *X* part and resonates at  $\sim 4.0$  ppm, indicating the formation of the 1,4-oxazine ring with two nonequivalent faces. The NMR proton COSY spectrum demonstrates a low interactions of the  $\text{O-CH}_2\text{-C=}$  protons with the triazolic proton, which appears as ordinary singlet at  $\sim 7.41$  ppm. This latter information confirms therefore the formation of 1,5-disubstituted, *exo*-cyclic isomer (**4**).

The ring opening azide ion reaction on polyoxyethylene dioxiranes (**1**), gives the corresponding di(azido-diols) (**2**). The *O*-propargylation of compounds **2**, yields the air unstable di(azido-alkynes) (**3**). The latter are thermally refluxed without catalyst in toluene to give rise to the unique tetraheterocyclic (1,5-disubstituted) *exo*-polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**). The synthesized *exo*-heterotetracyclic polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**) obtained from simple reagents can probably present some interesting applications in biological field. Compounds (**3**) are under investigations.

## EXPERIMENTAL

IR spectra were realized on Perkin Elmer Paragon 1000 PC spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were realized on a Bruker 300 spectrometer at 300 and 75 MHz respectively. TMS is the standard reference. HRMS spectra in C. I. mode, were carried out on a MAT 95 SBE spectrometer. All chemical are purchased from Sigma-Aldrich. Except for propargyl bromide, which is distilled, all other chemicals are used without further purification. The used silica gel is of the Merck 7734 type.

### Preparation of di(azido-alcohols) (**2**):

A solution of 32 mmol of polyoxyethylene di(oxirane) (**1**), 8 g of sodium azide, 2 g of ammonium chloride in 20 mL of water and 80 mL of MeOH was stirred for 24 h at 80 °C, then filtered. The MeOH was evaporated. The crude product was extracted with  $\text{Et}_2\text{O}$  (3 x 80 mL), washed with water and dried on  $\text{MgSO}_4$  and purified on chromatography column of silica gel. The mixture  $\text{EtOAc}/\text{Et}_2\text{O}$  (70/30) was used as eluant to obtain compounds (**2a-d**) as yellowish viscous oils.

### Synthesis of polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) (**4**):

To a mixture of water (0.25 mL), sodium hydroxide (3 g, 75 mmol), tetrabutylammonium hydrogen sulfate (0.1 g) and 75 mmol of propargyl bromide at 40 °C, 25 mmol of di(azido-alcohol) (**2**) were added. The mixture was stirred for 40 min at 40 °C. Then 50 mL of toluene were added, the mixture was filtered and the salt washed with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL).  $\text{CH}_2\text{Cl}_2$  and the propargyl bromide excess were evaporated

under vacuum. The obtained crude product (**3**) was diluted with toluene and heated to reflux for 24 h. Then toluene was distilled, the viscous obtained residue was purified on silica gel chromatography column. Et<sub>2</sub>O was used as eluent, yielding compounds (**4a-d**) as yellowish viscous oils (Table 2).

**1,2-Bis((6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6-yl)methoxy)ethane (4a):**

IR:  $\nu_{C=C} = 1454$ ,  $\nu_{N=N} = 1496$  cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 3.68-3.73 (m., 8H, 4CH<sub>2</sub>, O-CH<sub>2</sub>), 4.00 (m., 2H, 2CH, <sup>3</sup>J<sub>HH</sub> = 2.9 Hz), 4.13 and 4.47 (m., 4H, 2CH<sub>2</sub>-N, <sup>2</sup>J<sub>HH</sub> = 12.5 Hz, <sup>3</sup>J<sub>HH</sub> = 2.9 Hz), 4.75 and 5.54 (d.d., 4H, 2CH<sub>2</sub>-O, <sup>2</sup>J<sub>HH</sub> = 15.4 Hz), 7.40 (s, 2H, 2HC=); <sup>13</sup>C NMR (CDCl<sub>3</sub>),  $\delta$ : 46.8 (2C, 2CH<sub>2</sub>-N), 61.8 (2C, 2CH<sub>2</sub>-C=), 71.0 (4C, 2CH<sub>2</sub>-O), 72.6 (2C, 2CH), 127.8 (2C, 2HC=), 130.3 (2C, 2C=); HRMS: for C<sub>14</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub> Calcd: 336.15460, Found: 336.15490; Anal. Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub>: C, 49.99; H, 5.99; N, 24.99. Found: C, 49.92; H, 5.95; N, 24.95.

**6,6'-(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(methylene))bis(6,7-dihydro-4H-[1,2,3]triazolo[5,1-c]-[1,4] oxazine) (4b):**

IR:  $\nu_{C=C} = 1453$ ,  $\nu_{N=N} = 1495$  cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 3.65-3.71 (m., 12H, 6CH<sub>2</sub>-O), 3.99 (m., 2H, 2CH, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.12 and 4.46 (m., 4H, 2CH<sub>2</sub>-N, <sup>2</sup>J<sub>HH</sub> = 12.1 Hz, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.74 and 5.53 (d.d., 4H, 2CH<sub>2</sub>-O, <sup>2</sup>J<sub>HH</sub> = 15.2 Hz), 7.40 (s, 2H, 2HC=); <sup>13</sup>C NMR (CDCl<sub>3</sub>),  $\delta$ : 46.7 (2C, 2CH<sub>2</sub>-N), 61.5 (2C, 2CH<sub>2</sub>-C=), 70.6 (6C, 6CH<sub>2</sub>-O), 72.3 (2C, 2CH), 127.4 (2C, 2HC=), 129.9 (2C, 2C=); HRMS: for C<sub>16</sub>H<sub>24</sub>N<sub>6</sub>O<sub>5</sub> Calcd: 380.18082, Found: 380.18132 Anal. Calcd for C<sub>16</sub>H<sub>24</sub>N<sub>6</sub>O<sub>5</sub>: C, 50.52; H, 6.36; N, 22.09. Found: C, 50.39; H, 6.30; N, 22.02.

**1,12-Bis(6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6-yl)-2,5,8,11-tetraoxadodecane (4c):**

IR:  $\nu_{C=C} = 1454$ ,  $\nu_{N=N} = 1496$  cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 3.66-3.72 (m., 16H, 8CH<sub>2</sub>-O), 4.01 (m., 2H, 2CH, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.14 and 4.48 (m., 4H, 2CH<sub>2</sub>-N, <sup>2</sup>J<sub>HH</sub> = 12.2 Hz, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.74 and 5.52 (d.d., 4H, 2CH<sub>2</sub>-O, <sup>2</sup>J<sub>HH</sub> = 15.13 Hz), 7.42 (s, 2H, 2HC=); <sup>13</sup>C NMR (CDCl<sub>3</sub>),  $\delta$ : 46.9 (2C, 2CH<sub>2</sub>-N), 62.0 (2C, 2CH<sub>2</sub>-C=), 71.2 (8C, 8CH<sub>2</sub>-O), 72.9 (2C, 2CH), 128.0 (2C, 2HC=), 130.5 (2C, 2C=); HRMS: for C<sub>18</sub>H<sub>28</sub>N<sub>6</sub>O<sub>6</sub> Calcd: 424.20703, Found: 424.20743; Anal. Calcd for C<sub>18</sub>H<sub>28</sub>N<sub>6</sub>O<sub>6</sub>: C, 50.93; H, 6.65; N, 19.80. Found: C, 50.84; H, 6.59; N, 19.71.

**1,15-Bis(6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazin-6-yl)-2,5,8,11,14-pentaoxapentadecane (4d):**

IR:  $\nu_{C=C} = 1452$ ,  $\nu_{N=N} = 1493$  cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 3.65-3.72 (m., 20H, 10CH<sub>2</sub>, O-CH<sub>2</sub>), 4.01 (m., 2H, 2CH, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.11 and 4.45 (m., 4H, 2CH<sub>2</sub>-N, <sup>2</sup>J<sub>HH</sub> = 12.1 Hz, <sup>3</sup>J<sub>HH</sub> = 3.2 Hz), 4.74 and 5.53 (d.d., 4H, 2CH<sub>2</sub>-O, <sup>2</sup>J<sub>HH</sub> = 15.2 Hz), 7.42 (s, 2H, 2HC=); <sup>13</sup>C NMR (CDCl<sub>3</sub>),  $\delta$ : 47.0 (2C, 2CH<sub>2</sub>-N), 62.0 (2C, 2CH<sub>2</sub>-C=), 71.3 (10C, 10CH<sub>2</sub>-O), 72.9 (2C, 2CH), 128.1 (2C, 2HC=), 130.8 (2C, 2C=); HRMS: for C<sub>20</sub>H<sub>32</sub>N<sub>6</sub>O<sub>7</sub> Calcd: 468.23325, Found: 468.23385; Anal. Calcd for C<sub>20</sub>H<sub>32</sub>N<sub>6</sub>O<sub>7</sub>: C, 51.27; H, 6.88; N, 17.94. Found: C, 51.13; H, 6.82; N, 17.88.

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