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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 intramolecular cycloaddition.

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

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

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

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

The (Cu^{+} or Ru^{2+}) catalyzed azide-alkyne cycloaddition is the best known of the 1,3-dipolar cycloaddition reaction.[24,25] It constitute actually the backbones reaction of the ”Click Chemistry”.[26] While the

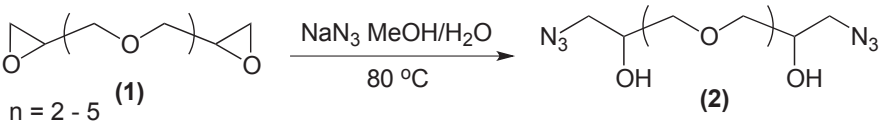
intramolecular cycloaddition presents a particular interest due to its potential use in the synthesis of polyheterocyclic systems,[27] it is very less described compared to the intermolecular one.[28] In the major cases the interest is focused on the target molecule rather than the mechanism, the structure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

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.[30] 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 cyloaddition, only diazides were reacted with dialkynes or *mono* azido-alkynes.[31] 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.[32]

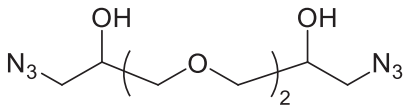
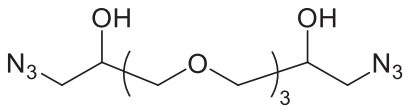
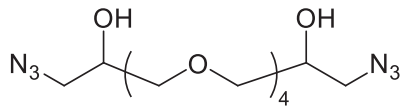
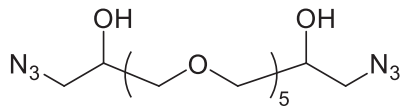
Herein we describe the synthesis of polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) via simple ring opening of the corresponding dioxiranes, followed by *O*-propargylation.

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



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

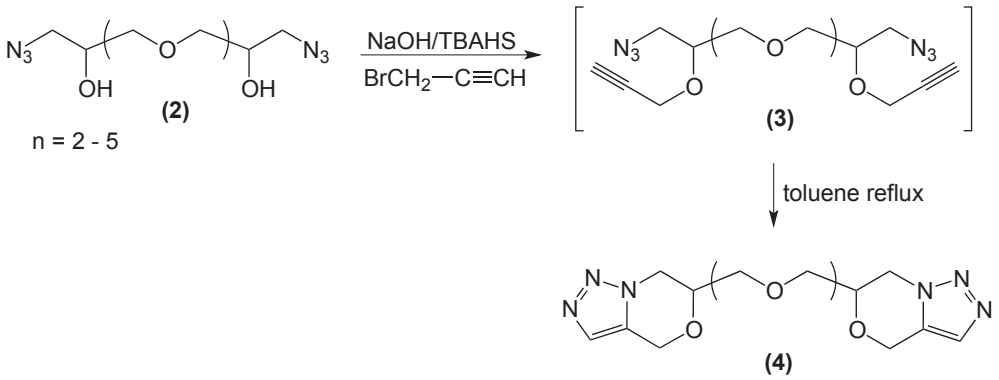
Table 1. Synthesized polyoxyethylene diazido-diols **(2)**

Entry	diazido-diols **(2)**		Y (%)
1		**(2a)**	80
2		**(2b)**	83
3		**(2c)**	86
4		**(2d)**	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,[33] 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.

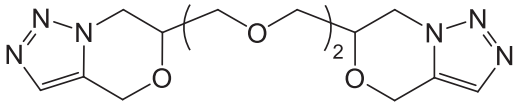
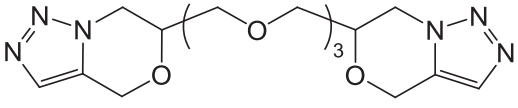
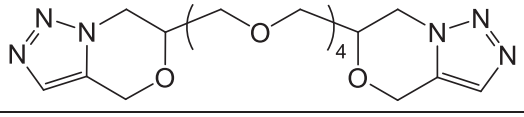
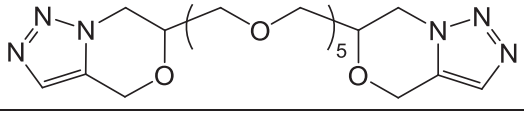
As a direct application, compounds **(3)** were heated in the same solvent, without catalyst. An intramolecular 1,3-dipolar cycloaddition occurs, yielding exclusively the stable 1,5-disubstituted *exo*-tetraheterocyclic polyoxyethylene di(1,2,3-triazolo-1,4-oxazines) **(4)** (Scheme 2).



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) **(4)**		Y (%)
5		**(4a)**	83
6		**(4b)**	83
7		**(4c)**	85
8		**(4d)**	88

Compounds **(2** and **4)** were identified by IR, ^{1}H and ^{13}C NMR spectroscopies, as well as by HRMS and elementary analysis. On the ^{1}H NMR spectrum of compounds **(4)**, the two allylic protons O-CH_2-C= constitute an *AB* system resonating at ~ 5 ppm, ($^{2}J_{AB}$ ~ 15 Hz). Two other protons CH_2-N are also non equivalent and constitute the *AB* part of an *ABX* system ($^{2}J_{AB}$ ~ 12 Hz), with the proton of the asymmetric carbon atom HC*, constitute the *X* part and resonates at ~ 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 O-CH_2-C= protons with the triazolic proton, which appears as ordinary singlet at ~ 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}H and ^{13}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 Et_2O (3 x 80 mL), washed with water and dried on $MgSO_4$ and purified on chromatography column of silica gel. The mixture EtOAc/Et_2O (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 CH_2Cl_2 (3 x 20 mL). CH_2Cl_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_2O was used as eluent, yielding compounds **(4a-d)** as yellowish viscous oils (Table 2).

1,2-Bis((6,7-dihydro-4*H*-[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^{-1}; ^1H NMR ($CDCl_3$), δ: 3.68-3.73 (m., 8H, $4CH_2$, O-CH_2), 4.00 (m., 2H, 2CH, $^3J_{HH}$ = 2.9 Hz), 4.13 and 4.47 (m., 4H, $2CH_2$-N, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 2.9 Hz), 4.75 and 5.54 (d.d., 4H, 2CH_2-O, $^2J_{HH}$ = 15.4. Hz), 7.40 (s, 2H, 2HC=); ^{13}C NMR ($CDCl_3$), δ: 46.8 (2C, 2$\underline{C}H_2$-N), 61.8 (2C, 2$\underline{C}H_2$-C=), 71.0 (4C, 2$\underline{C}H_2$-O), 72.6 (2C, 2$\underline{C}$H), 127.8 (2C, 2H$\underline{C}$=), 130.3 (2C, 2$\underline{C}$=); HRMS: for $C_{14}H_{20}N_6O_4$ Calcd: 336.15460, Found: 336.15490; Anal. Calcd for $C_{16}H_{20}N_6O_4$: 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-4*H*-[1,2,3]triazolo[5,1-*c*]-[1,4] oxazine) (4b):

IR: $\nu_{C=C}$ = 1453, $\nu_{N=N}$ = 1495 cm^{-1}; ^1H NMR ($CDCl_3$), δ: 3.65-3.71 (m., 12H, $6CH_2$-O), 3.99 (m., 2H, 2CH, $^3J_{HH}$ = 3.2 Hz), 4.12 and 4.46 (m., 4H, $2CH_2$-N, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 3.2 Hz), 4.74 and 5.53 (d.d., 4H, 2CH_2-O, $^2J_{HH}$ = 15.2 Hz), 7.40 (s, 2H, 2HC=); ^{13}C NMR ($CDCl_3$), δ: 46.7 (2C, 2$\underline{C}H_2$-N), 61.5 (2C, 2$\underline{C}H_2$-C=), 70.6 (6C, 6$\underline{C}H_2$-O), 72.3 (2C, 2$\underline{C}$H), 127.4 (2C, 2H$\underline{C}$=), 129.9 (2C, 2$\underline{C}$=); HRMS: for $C_{16}H_{24}N_6O_5$ Calcd: 380.18082, Found: 380.18132 Anal. Calcd for $C_{16}H_{24}N_6O_5$: 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-4*H*-[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^{-1}; ^1H NMR ($CDCl_3$), δ: 3.66-3.72 (m., 16H, $8CH_2$-O), 4.01 (m., 2H, 2CH, $^3J_{HH}$ = 3.2 Hz), 4.14 and 4.48 (m., 4H, $2CH_2$-N, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 3.2 Hz), 4.74 and 5.52 (d.d., 4H, 2CH_2-O, $^2J_{HH}$ = 15.13 Hz), 7.42 (s, 2H, 2HC=); ^{13}C NMR ($CDCl_3$), δ: 46.9 (2C, 2$\underline{C}H_2$-N), 62.0 (2C, 2$\underline{C}H_2$-C=), 71.2 (8C, 8$\underline{C}H_2$-O), 72.9 (2C, 2$\underline{C}$H), 128.0 (2C, 2H$\underline{C}$=), 130.5 (2C, 2$\underline{C}$=); HRMS: for $C_{18}H_{28}N_6O_6$ Calcd: 424.20703, Found: 424.20743; Anal. Calcd for $C_{18}H_{28}N_6O_6$: 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-4*H*-[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^{-1}. ^1H NMR ($CDCl_3$), δ: 3.65-3.72 (m., 20H, $10CH_2$, O-CH_2), 4.01 (m., 2H, 2CH, $^3J_{HH}$ = 3.2 Hz), 4.11 and 4.45 (m., 4H, $2CH_2$-N, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 3.2 Hz), 4.74 and 5.53 (d.d., 4H, 2CH_2-O, $^2J_{HH}$ = 15.2 Hz), 7.42 (s, 2H, 2HC=); ^{13}C NMR ($CDCl_3$), δ: 47.0 (2C, 2$\underline{C}H_2$-N), 62.0 (2C, 2$\underline{C}H_2$-C=), 71.3 (10C, 10$\underline{C}H_2$-O), 72.9 (2C, 2$\underline{C}$H), 128.1 (2C, 2H$\underline{C}$=), 130.8 (2C, 2$\underline{C}$=); HRMS: for $C_{20}H_{32}N_6O_7$ Calcd: 468.23325, Found: 468.23385; Anal. Calcd for $C_{20}H_{32}N_6O_7$: C, 51.27; H, 6.88; N, 17.94. Found: C, 51.13; H, 6.82; N, 17.88.

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