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Failure to synthesize 1,5-disubstituted *endo*-heterobicyclic 1,2,3-Triazolo-1,4-Oxazines

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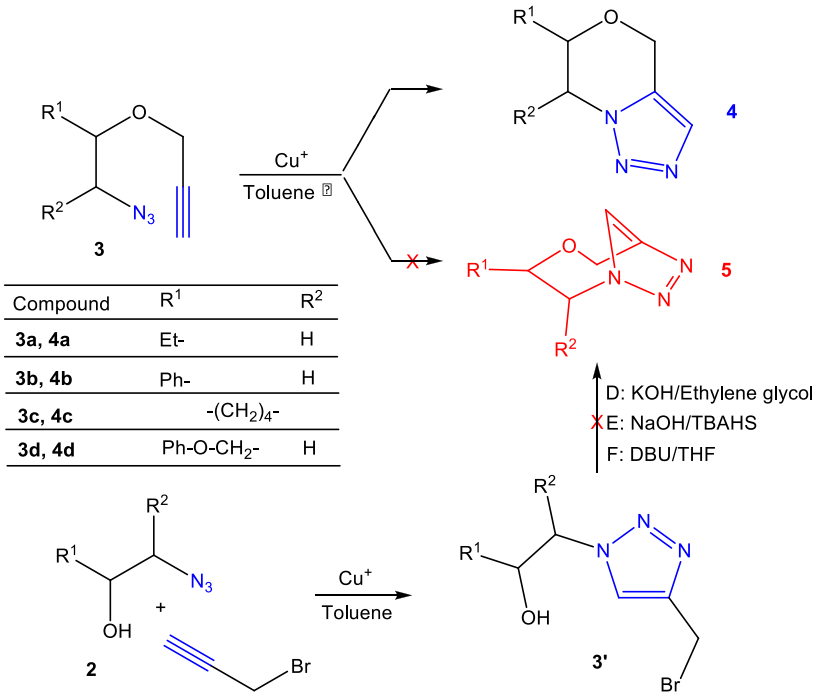
Graphical Abstract



Compound	R^1	R^2
3a, 4a	Et-	H
3b, 4b	Ph-	H
3c, 4c	$-(CH_2)_4-$	
3d, 4d	Ph-O-CH_2-	H

Abstract: The synthesis of *endo*-polyheterocyclic bridged 1,2,3-triazolo-1,4-oxazine isomers from azido-alkynes was attempted. In the non-catalyzed reaction, only the *exo*-heteropolycyclic fused isomers were obtained. When Cu(I) was used as a catalyst or in an equimolar ratio, no effect on the reaction orientation was observed. The bridged isomer was also not obtained via another synthetic route in which the reaction order was reversed to yield the corresponding bromo-triazolo-alcohol. In addition, the cycloetherification step leads instead to the formation of the polymeric product.

Keywords: Intramolecular cycloaddition, Triazolo-oxazine, 1,4-Oxazine, Azido-alkyne, 1,2,3-triazole, *endo*-bicyclic.

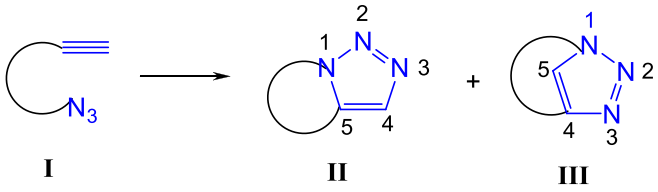
Introduction

1,2,3-Triazoles and oxazines constitute two interesting varieties of heterocyclic compounds that give rise to a large number of synthetic compounds.[1-4] The applications of these heterocycles have been reported in various areas.[5-9] The use of catalytic regioselective methods has a remarkable effect on the development of the 1,3-dipolar azide-alkyne cycloaddition.[10] The majority of the studies involve intermolecular cycloadducts[11], however those related to the intramolecular processes remain limited.[12,13] These intramolecular reactions have focused on the synthesis of target and specific molecules, rather than on a general systematic investigation of its potential applications in organic synthesis. [12, 14]

The non-catalyzed intermolecular azide/alkyne cycloaddition reaction gives a mixture of 1,2,3-triazoles 1,4- and 1,5-disubstituted.[15] The corresponding catalyzed reaction leads exclusively to the 1,4 or 1,5-disubstituted 1,2,3-triazoles in the presence of Cu^{+} [16] or Ru^{2+} [17], respectively.

For the intramolecular cycloaddition reaction shown in Scheme 1, two possible bicyclic isomers can be formed depending on the number of bonds between the azide and alkyne functions. The azido-alkyne **I** can lead to either the 1,5-disubstituted (*exo*-cyclic, **II**) or the 1,4-disubstituted (*endo*-cyclic, **III**) triazole or both of them. [18]

The *exo*-cyclic isomer **II** is spontaneously favored to obtain then the *endo*-cyclic isomer **III** because of the geometrical constraints.



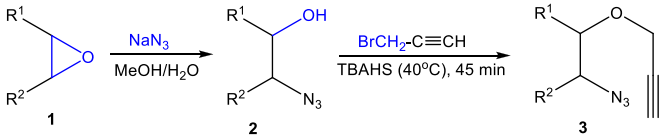
Scheme 1: Intramolecular azido-alkyne cycloaddition.

Herein, the opening reaction of oxirane rings was followed by a series of simple reactions which correspond to an intramolecular cycloaddition leading to the 1,5-disubstituted (*exo*-cyclic) fused 1,2,3-triazolo-1,4-oxazines. [19]

In an attempt to obtain the 1,4-disubstituted isomer (*endo*-) and therefore to see whether the Cu^{+} catalyst could permit to overcome the geometrical constraints, we used Cu(I) as catalyst in the intramolecular azide/alkyne cycloaddition reaction. The intramolecular cycloetherification reaction of the corresponding bromo-triazolo-alcohol was also attempted to synthetically obtain the *endo*-cyclic isomer.

Results and discussion

The preparation of azido-alkyne ethers was achieved with the oxirane ring opening reaction by azide ion followed by the action of propargyl bromide (Scheme 2). Azido-alkyne ethers **3** were prepared in satisfactory yields and the results are summarized in Table I.



Compound	R^1	R^2
1a, 2a, 3a	Et-	H
1b, 2b, 3b	Ph-	H
1c, 2c, 3c	-$(CH_2)_4$-	
1d, 2d, 3d	Ph-O-CH_2-	H

TBAHS: Tetrabutylammonium Hydrogenosulfate

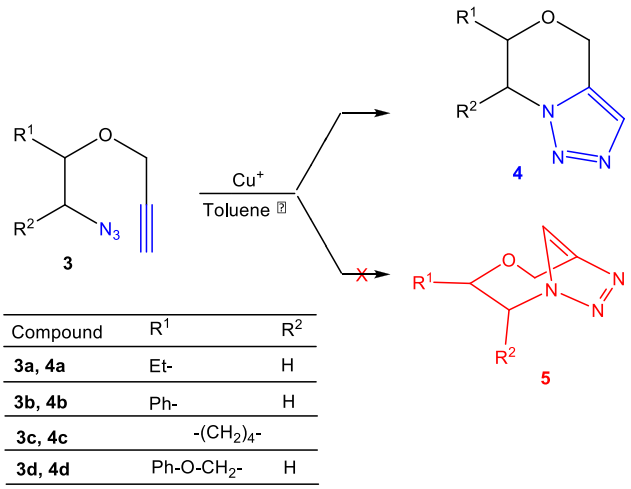
Scheme 2: Synthesis of azido-alkyne derivatives.

Table I : Synthesized azido-alkyne ethers **3**.

Entry	Azido-alcohol **2**	Azido-alkyne ethers **3**	Y (%)
1	**2a**	**3a**	87
2	**2b**	**3b**	88
3	**2c**	**3c**	83
4	**2d**	**3d**	89

The uncatalyzed cycloaddition reaction is spontaneously possible at room temperature and leads to the *exo*-cyclic isomer **4**, but it is kinetically slow.[19] In order to increase its rate, the reaction was carried out at refluxing toluene (*Condition A* [20]). Compounds **4** were obtained in satisfactory yields and the results were summarized in table II.

In an attempt to reverse the reaction orientation towards the formation of the *endo*-cyclic isomer **5**, the reaction was performed in the presence of a catalytic amount of Cu^{+} (*Condition B* [21]) and the corresponding cuprous alkynide (*Condition C* (**3b**) [22]) at reflux in toluene (Scheme 3).



Compound	R^1	R^2
3a, 4a	Et-	H
3b, 4b	Ph-	H
3c, 4c	-$(CH_2)_4$-	
3d, 4d	Ph-O-CH_2-	H

Scheme 3: Reaction in favor of the formation of the fused bicyclic isomer **4** as a single product in *A*, *B* and *C* conditions

When carried out under conditions *A*, *B* and *C*, (three times for *B* and *C* conditions), the intramolecular cycloaddition of azido-alkyne ethers **3** leads to the formation of the unique isomer **4**.

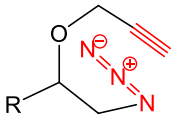
Table II: Synthesized 1,2,3-triazolo-1,4-oxazines **4** from *A*, *B* and *C* conditions.

Entry	1,2,3-Triazolo-1,4-oxazines **4**	*A* (Y %)	*B* (Y %)	*C* (Y %)
1	**4a**	89	85	-
2	**4b**	90	88	85
3	**4c**	86	85	-
4	**4d**	88	84	-

The *exo*-cyclic compounds **4a-d** were fully characterized by spectroscopic techniques: IR, ^{1}H and ^{13}C NMR, and HRMS.

The ^{1}H NMR spectra confirm the proposed cyclic structures which revealed an *AB* system corresponding to the two allylic protons O-CH_2-C=C, appearing approximately into 5.0 ppm with a coupling constant $^2J_{AB}$ = 15 Hz. For acyclic compounds, the same protons appear as a singlet more shifted to high fields (~ 4.6 ppm).[23] This difference may be explained by the magnetic nonequivalence of these two cyclic protons. Moreover, the protons CH_2-N are also nonequivalent and show another *AB* system ($^2J_{AB}$ ~ 12 Hz) which is partially coupled with the proton of the asymmetric carbon. The chemical shift and the nature of the signal vary according to the corresponding structure. The ^{1}H NMR data of the *exo*-cyclic isomer **4** and *endo*- one **5** (Scheme 5) are theoretically similar. To confirm the formation of the structure **4,** we used COSY NMR technique in which the spectra indicate that the triazolic proton interacts only with the two allylic ones, confirming the formation of the *exo*-cyclic isomer **4**.

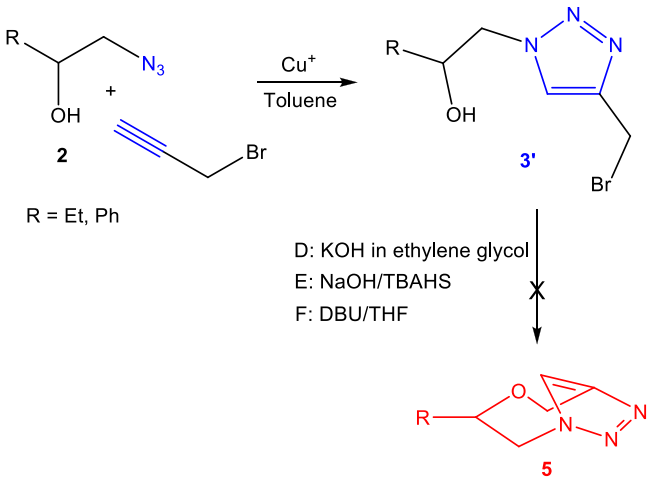
To form the isomer **5**, the two dipoles (azide and alkyne) should be close enough to each other as shown in Scheme 4. This special arrangement is hard to be realized which may explain the non formation of these products.



Scheme 4: Suggested arrangement to obtain the bridged bicyclic isomer **5**.

Another synthetic route (Scheme 5) attempting to get the *endo*-cyclic compounds **5** consisted in the inversion of the reactions order. First, the [3+2] intermolecular cycloaddition between the azido-alcohol **2** and propargyl bromide was done to obtain the bromo-triazolo-alcohol **3'** in good yield (~ 80 %). It was followed by attempts at an intramolecular cycloetherification[24] in the presence of three different bases, three times for each one. Whatever the used bases: KOH in ethylene glycol (*Condition D* [25]), NaOH in the presence of transfer phase catalyst TBAHS (*Condition E* [26]) and DBU in THF (*Condition F* [27]), the reaction leads only to the formation of a polymeric product no trace of the isomer **5** was observed.

The rigidity of the structure of the triazolic compounds **3'** may explain why the cycloetherification reaction did not take place. The IR spectra of the obtained viscous oil showed no signal related to the hydroxyl group (OH). The ^{1}H NMR spectra are similar to those of the bromo hydroxyl triazole with disappearance of the alcoholic proton signal. The triazolic proton shift (δ ~ 7.57 ppm) and the absence of the interactions between the triazolic protons and the protons CH_2-N in the COSY NMR spectra, demonstrated the non formation of compounds **5**.



Scheme 5: Failure synthesis of the bridged isomer **5** via the bromo-triazolo-alcohol **3'**.

Thus the spectroscopic data, as well as the data obtained from the preliminary size-exclusion chromatography tests justify the formation of the polymeric products.

Conclusions

The exclusive formation of the *exo*-cyclic fused isomer **4** according to *A, B* and *C* conditions shows that neither the absence of Cu^+ nor its presence in catalytic or stoichiometric amounts did not permit the reverse orientation of the reaction in favor of the bridged *endo*-cyclic isomer **5**, presumably due to geometric constraints. This isomer also cannot be obtained from the corresponding bromo-triazolo-alcohol **3'** which leads to formation of the polymeric product in the intramolecular cycloetherification step. The viscous polymeric products obtained are under investigation. This failure encourages us to search for new synthetic routes to these compounds such as electrochemical synthesis.

Experimental

IR spectra were realized on Perkin Elmer Paragon 1000 PC spectrometer. The NMR ^{1}H and ^{13}C spectra were realized on a Bruker AC 300 spectrometer respectively at 300 and 75 MHz. The TMS was used as a standard reference for ^{1}H and ^{13}C NMR spectra. HRMS spectra were realized on a MAT 95 SBE spectrometer in C. I. mode. The silica gel was a Merck 7734. Oxiranes, sodium azide, propargyl bromide, and solvents are the products of the Fluka society.

Preparation of azido-alcohols **2**: A solution of 8 mmol of oxirane, 2 g of sodium azide, 0.5 g of ammonium chloride in 5 mL of water and 20 mL of methanol was stirred for 16 h at 80 °C, then filtered and the methanol was evaporated. The mixture was extracted with diethyl ether (3 x 80 mL), washed with water and dried on $MgSO_4$, purified on silica gel chromatographic column, using diethyl ether as eluant to obtain pure compounds **2**.

1-azidobutan-2-ol (***2a***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ : 0.98 (t, 3H, CH_3-, $^{3}J_{HH}$ = 7.1 Hz), 1.65 (m, 2H, CH_3-CH_2, $^{3}J_{HH}$ = 7.1 Hz), 3.35 (m, 2H, CH_2-N_3), 4.80 (m, 1H, C*H*), 3.31 (l.s., 1H, OH); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 10.8 (1C, *C*H_3-), 30.0 (1C, *C*H_2), 74.8 (1C, *C*H), 62.3 (1C, *C*H_2-N_3).

2-azido-1-phenylethanol (***2b***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ : 2.40 (d, 1H, OH), 3.45 (m., 2H, CH_2-N), 4.90 (m, 1H, C*H*), 7.35 (m, 5H, C*H arom*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 60.9 (1C, *C*H_2-N_3), 74.2 (1C, *C*H-O), 127.9 (2C, 2*C*H *arom*), 128.4 (1C, *C*H *arom*), 129.7 (2C, 2*C*H *arom*), 141.4 (1C, *C arom*).

2-azidocyclohexanol (***2c***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ: 1.31 (m, 4H, 2CH_2), 1.75 (m, 2H, CH_2), 2.04 (m, 2H, *CH*$_2$), 2.31 (l.s., 1H, OH), 3.18 (m, 1H, C*H*-O), 3.39 (m, 1H, C*H*-N_3); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 23.8 (1C, *C*H_2), 24.2 (1C, *C*H_2), 29.7 (1C, *C*H_2), 33.1, (1C, *C*H_2), 67.1, (1C, *C*H-N_3), 73.8 (1C, *C*H-OH).

1-azido-3-phenoxypropan-2-ol (***2d***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ: 3.50 (m, 2H, CH_2-N_3), 3.93 (m, 1H, OH), 4.00 (d, 2H, CH_2-O), 4.18 (s, 1H, C*H*-O), 6.95-7.36 (m, 5H, C*H arom*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 60.5 (1C, *C*H_2-N_3), 69.2, (1C, *C*H_2-O), 69.3 (1C, *C*H), 114.3 (2C, 2*C*H *arom*), 121.2 (1C, *C*H *arom*), 129.4 (2C, 2*C*H *arom*), 158.4 (1C, *C arom*).

Synthesis of azido-alkynes ***3****:* To a vigorously stirred mixture of sodium hydroxide (6 g, 0.15 mol), water (0.5 mL), tetrabutylammonium hydrogensulfate (TBAHS) (0.2 g) and azido alcohol **2** (25 mmol) at 40 °C, 0.15 mol of propargylbromide was added. After 45 min, the mixture was filtered and the salt was washed with methylene chloride (2 x 25 mL). The volatiles were evaporated and the crude product was purified on silica gel chromatography column using petroleum ether, then dichloromethane to obtain liquid compounds **3**.

1-azido-2-(prop-2-ynyloxy)butane (***3a***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ: 1.05 (t, 3H, CH_3-, $^{3}J_{HH}$ = 7.5 Hz), 1.72 (m, 2H, CH_3-CH_2, $^{3}J_{HH}$ = 7.5 Hz), 2.50 (t, 1H, ≡C*H*, $^{4}J_{HH}$ = 2.5 Hz), 3.53 (d.d, 2H, CH_2-N_3), 4.21 (d.d, 2H, CH_2-C≡, $^{2}J_{HH}$ = 15.2 Hz, $^{4}J_{HH}$ = 2.5 Hz), 4.75 (m, 1H, C*H*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 10.9 (1C, *C*H_3-), 25.7 (1C, *C*H_2), 60.1 (1C, *C*H_2-N_3), 56.6 (1C, *C*H_2-O), 77.5 (1C, ≡*C*H), 79.8 (1C, *C*≡), 81.3 (1C, *C*H-O).

(2-azido-1-(prop-2-ynyloxy)ethyl)benzene (***3b***) *:* ^{1}H *NMR (*$CDCl_3$*),* δ: 2.55 (t, 1H, ≡C*H*, $^{4}J_{HH}$ = 2.4 Hz), 3.49 (d.d, 2H, CH_2-N_3, $^{2}J_{HH}$ = 12.6 Hz), 4.25 (d.d, CH_2-C≡, $^{2}J_{HH}$ = 15.1 Hz, $^{4}J_{HH}$ = 2.4 Hz), 4.79 (m, 1H, C*H*-O), 7.28-7.41 (m, 5H, C*H arom*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 60.9 (1C, *C*H_2-N_3), 56.4 (1C, O-*C*H_2), 74.9 (1C, ≡*C*H), 79.1 (1C, *C*≡), 79.8 (1C, *C*H-O), 127.0 (2C, *C*H *arom*), 127.2 (1C, *C*H *arom*), 128.6 (1C, *C*H *arom*), 128.9 (1C, *C arom*), 129.1 (1C, C *arom*), 137.6 (1C, *C arom*).

1-azido-2-(prop-2-ynyloxy)cyclohexane (***3c***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ: 1.29 (m, 4H, 2CH_2 *Cyclohexyl*), 1.75 (m, 2H, CH_2, *Cyclohexyl*), 1.89 (m, 2H, *CH*$_2$ *Cyclohexyl*), 2.65 (s, 1H, ≡C*H*), 3.20 (m, 1H, C*H*-O), 3.45 (m, 3H, C*H*-N_3 & O-CH_2-C≡); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 22.8 (2C, 2CH_2 *Cyclohexyl*), 23.7 (2C, 2CH_2, *Cyclohexyl*), 29.6 (2C, 2*C*H), 33.0 (1C, *C*H_2-O), 66.9 (1C, ≡*C*H), 73.4 (1C, ≡*C*).

(3-azido-2-(prop-2-ynyloxy)propoxy)benzene (***3d***)*:* ^{1}H *NMR (*$CDCl_3$*),* δ: 2.53 (t, 1H, ≡C*H*), 3.60 (d, 2H, CH_2-N_3), 4.00 (d, 2H, CH_2-O), 4.18 (l.s, 1H, C*H*-O), 4.35 (2H, O-CH_2), 6.95-7.36 (m, 5H, C*H arom*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 59.4 (1C, *C*H_2-N_3), 57.4 (1H, *C*H_2-O), 68.2, (1C, *C*H_2-O), 68.3 (1C, *C*H), 78.6 (1C, ≡*C*H), 81.3 (1C, ≡*C*), 114.3 (2C, 2*C*H *arom*), 121.2 (1C, 1*C*H *arom*), 129.4 (2C, 2*C*H *arom*), 158.4 (1C, *C arom*).

1,3-dipolar intramolecular cycloaddition: A solution of 2,5 mmol of azido-alkyne **3** (*A* without Cu^{+}), (*B* : 5 % Cu^{+}) or azido cuprous alkynide for compound **3b** (*C* : 100 % Cu^{+}) in toluene (15 mL) was heated at reflux for 24 h, then filtered and the toluene was evaporated. The crude was purified on silica gel chromatography column using petroleum ether to eliminate impurities, then a mixture of petroleum ether/diethyl ether (70/30), to obtain compounds **4** as viscous oil or solid.

6-ethyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4] oxazine (***4a***)*: IR (*$CHCl_3$*):* $\nu_{C=C}$ = 1454, $\nu_{N=N}$ = 1499 cm^{-1}; ^{1}H *NMR (*$CDCl_3$*),* δ: 1.09 (t, 3H, CH_3, $^{3}J_{HH}$ = 7.5 Hz), 1.76 (q.d, 2H, CH_2-CH_3), 3.77 (m, 1H, CH_2-C*H*-O), 4.23 (d.m, 2H, CH-CH_2-N, $^{2}J_{HH}$ = 12 Hz), 4.94 (d.d, 2H, O-CH_2-C=, $^{2}J_{HH}$ = 16.5 Hz), 7.46 (s, 1H, =C*H*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 9.41 (1C, *C*H_3-), 25.93 (1C, CH_3-*C*H_2), 49.52 (1C, *C*H_2-N), 61.76 (1C, O-*C*H_2-C=), 74.95 (1C, O-*C*H-CH_2), 127.77 (1C, *C*=), 130.70 (1C, =*C*H); *HRMS : Calculated:* 153.09029, *Found:* 153.08989, *Δ(umm):* -0.4.

6-phenyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4] oxazine (***4b***)*: mp* = 135 °*C; IR (KBr):* $\nu_{C=C}$ = 1454, $\nu_{N=N}$ = 1499 cm^{-1}; ^{1}H *NMR (*$CDCl_3$*),* δ*:* 4.03 (d.m, 2H, CH-CH_2-N, $^{2}J_{HH}$ = 12 Hz, $^{3}J_{HH}$ = 4.5 Hz), 4.91 (d.d, 2H, O-CH_2-C=, $^{2}J_{HH}$ = 15 Hz), 5.54 (t, 1H, O-C*H*, $^{3}J_{HH}$ = 4.5 Hz), 7.04- 7.28 (m, 5H, C*H arom*), 7.54 (s, 1H, =C*H*); ^{13}C *NMR (*$CDCl_3$*),* δ*:* 50.9, (*C*H_2-N), 62.1 (*C*H_2-O), 75.5 (*C*H), 125.9, 126.1, 128.0, 128.6, 128.8, 128.9, 136.7 (7*C, C arom*), 130.2 (1C, =*C*H); *HRMS: Calculated:* 201.09029, *Found:* 201.09059, *Δ(umm):* +0.3.

5a,6,7,8,9,9a-hexahydro-4H-[1,2,3]triazolo[1,5-d][1,4] oxazine (***4c***)*: mp* = 101 °*C: IR (*$CHCl_3$*):* $\nu_{C=C}$ = 1453, $\nu_{N=N}$ = 1495 cm^{-1}; ^{1}H *NMR (*$CDCl_3$*),* δ*:* 1.45-1.61 (m, 4H, 2CH_2, *Cyclohex*), 1.93 (m, 2H, CH_2, *Cyclohex*), 2.17 (d.m, 1H, C*H*, *Cyclohex*, $^{2}J_{HH}$ = 12.5 Hz), 3.01 (d.m, 1H, C*H*, *Cyclohex*, $^{2}J_{HH}$ = 12.5 Hz), 3.43 (m, 1H, CH_2-C*H*-O), 3.94 (t.m, 1H, CH_2-C*H*-N), 4.99 (d. d, 2H, O-CH_2-C=, $^{2}J_{HH}$ = 15.1 Hz), 7.48 (s, 1H, =C*H*); ^{13}C *NMR (*$CDCl_3$*):* δ 23.98 (2C, *C*H_2 *Cyclohex*), 28.24 (1C, *C*H_2, *Cyclohex*), 30.43 (1C, *C*H_2, *Cyclohex*), 61.30 (1C, O-*C*H-CH_2-N), 62.47 (1C, O-*C*H_2-C=), 78.79 (1C, O-*C*H_2), 128.5 (1C, =*C*), 132.1 (1C, =*C*H);

HRMS Calculated: 179,10594*, Found:* 179,10644*, Δ(umm) :+0.4*.

*6-phenyloxymethyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c] [1,4]oxazine (**4d**): mp* = 141 °*C; IR (KBr):* $\nu_{C=C}$ = 1451, $\nu_{N=N}$ = 1496 cm^{-1}; ^{1}H *NMR (CDCl₃), δ:* 3.98 (d.m, 2H, CH-CH_2-N, $^{2}J_{HH}$ = 11.8 Hz, $^{3}J_{HH}$ = 4.0 Hz), 4.85 (d.d, 2H, O-CH_2-C=, $^{2}J_{HH}$ = 14.8 Hz), 5.45 (m, 1H, O-C*H*, $^{3}J_{HH}$ = 4.0 Hz), 4.12 (d.d, 2H, Ph-O-CH_2), 7.00-7.35 (m, 5H, C*H*, *arom*), 7.54 (s, 1H, =C*H*); ^{13}C *NMR (CDCl₃), δ:* 57.3 (1C, *C*H_2-N), 63.4 (1C, *C*H_2-O), 66.1 (1C, CH_2-O), 79.1 (1C, CH-O), 114.2 (2C, 2*C*H *arom*), 120.8 (1C, 1*C*H), 129.1 (1C, N-*C*=), 129.9 (2C, 2*C*H *arom*), 142.8 (1*C, =C*H), 159.9 (1C, 1*C arom*); *HRMS: Calculated:* 231.10078, *Found:* 231.10126, *Δ(umm):* -0.5.

Preparation of azido cuprous alkynide used in the method (C): An aqueous ammoniacal solution of 1.0 g (10.15 mmol) of cuprous chloride was poured with stirring into a solution of 2.04 g (10.15 mmol) of azido-alkyne **3b** in 100 mL of ethanol. The reaction mixture was allowed to stand for 15 min. The bright chartreuse precipitate was filtered off and washed five times each with water, ethanol and diethyl ether. The bright canary yellow solid thus obtained was dried in rotary evaporator at 50 °C (20 mmHg) for 2 h (70 %).

*Synthesis of bromo-triazolo-alcohol **3'**:* A mixture of propargyl bromide (11 mmol), azido alcohol **2** (10 mmol) and 10 mg of CuCl in 15 mL of dry toluene was heated at 70 °C for 16 h. The toluene and excess of propargyl bromide were evaporated, the crude product was purified on silica gel chromatography column, using a mixture of ethyl acetate/acetone (80/20) as eluant to obtain the compound **3'** as viscous oils (~80 %).

*1-(4-(bromomethyl)-1H-1,2,3-triazol-1-yl)butan-2-ol (**3'**):* ^{1}H *NMR (CDCl₃), δ*: 0.95 (t, 3H, CH_3-, $^{3}J_{HH}$ = 7.2 Hz), 1.52 (m, 2H, CH_3-CH_2-, $^{3}J_{HH}$ = 7.2 Hz), 3.35 (m, 1H, C*H*-O), 3.65 (l.s, 1H, OH), 3.82 (d.d, 1H, $^{2}J_{HH}$ = 14.8 Hz), 4.08 (d.d, 1H, $^{2}J_{HH}$ = 14.8 Hz), 4.62 (s, 2H, CH_2-Br), 7.58 (s, 1H, =C*H*); ^{13}C *NMR (CDCl₃), δ:* 10.7 (1C, *C*H_3-), 28.9 (1C, *C*H_2-Br), 29.3 (1C, CH_3-*C*H_2-), 61.9 (1C, *C*H_2-N), 70.8 (1C, *C*H-O), 124.1 (1C, =*C*H), 131.9 (1C, =*C*).

*2-(4-(bromomethyl)-1H-1,2,3-triazol-1-yl)-1-phenylethanol (**3'b**):* ^{1}H *NMR (CDCl₃), δ*: 1.05 (t, 3H, CH_3, $^{3}J_{HH}$ = 7.2 Hz), 1.70 (m, 2H, CH_3-CH_2, $^{3}J_{HH}$ = 7.2 Hz), 3.65 (l.s, 1H, OH), 3.82 (d.d, 2H, CH_2-N, $^{2}J_{HH}$ = 12.8 Hz), 4.45 (m, 1H, C*H*-O), 4.62 (s, 2H, CH_2-Br), 7.56 (s, 1H, =C*H*); ^{13}C *NMR (CDCl₃), δ:* 10.7 (1C, *C*H_3-), 28.9 (1C, *C*H_2-Br), 29.3 (1C, *C*H_2-CH_3), 61.9 (1C, *C*H_2-N), 70.8 (1C, *C*H-O), 124.1 (1C, =*C*H), 131.9 (1C, =*C*).

Cycloetherification reaction tests on bromo-triazolo-alcohol **3'**:

Condition C: 15 mL of ethylene glycol and 3 g of KOH were heated at 80 °C for 15 mn, then the mixture was returned to room temperature, 10 mmol of bromo-triazolo-alcohol **3'** were added slowly. Then the mixture was heated at 100 °C for 24 h under TLC control. At the end of the reaction the mixture was cooled down to room temperature. The mixture was washed with water to remove ethylene glycol. The viscous obtained crud was purified by silica gel column chromatography using methanol as eluant to obtain a mixture of oligomers.

Condition D: To a vigorously stirred mixture of 1,2 g of NaOH, 0.2 mL of water and 0.03 g of TBAHS, 10 mmol of bromo-triazolo-alcohol **3'** were added slowly. The mixture was maintained at 50 °C for 4 h. At the end of the reaction the mixture was cooled down to room temperature. The obtained crud was purified by silica gel column chromatography using methanol as eluant to obtain a mixture of oligomers.

Condition E: 5 mmol of bromo-triazolo-alcohol **3'** were dissolved in 20 mL of dry THF, then 6 mmol of DBU were slowly added. The mixture was then heated at 60 °C for 12 h. It was washed with a 10 % HCl solution, extracted with diethyl ether. The obtained viscous crud was purified by passage on silica gel column using methanol as eluant to obtain a mixture of oligomers.

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References

1. (a) Qian, W.; Winternheimer, D.; Amegadzie, A.; Allen, J., *Tetrahedron Lett.,* **2012***, 53 (3)*, 271-274; (b) Brown, A.; Ngai, T. Y.; Bames, M. A.; Key, J. A.; Cairo, C. W., *J. Phy. Chem. A.*, **2012**, *116, (1)*, 46-54.

2. (a) Stefani, H. A.; Amaral, M. F. Z. J.; Manarin, F.; Ando, R. A.; Silva, N. C. S.; Juaristi, E., *Tetrahedron Lett*., **2011**, *52 (51)*, 6883-6886; (b) Stanley, N. J.; Pedersen, D. S.; Nielsen, B.; Kvist, T.; Mathiesen, J. M.; Brauner-Osbome, H.; Taylor, D. K.; Abell, A. D., *Bioorg, Med. Chem. Lett.*, **2010**, *20, (24)*, 7512-7515.

3. Mueller, R.; Li, Y. X.; Hampson, A.; Zhong, S.; Harris, C.; Marrs, C.; Rachwal, R.; Ulas, J.; Nielsson, L.; Rogers, G., *Bioorg. Med. Chem. Lett*., **2011**, *21 (13)*, 3923-3926.

4. (a) Benaamane, N.; Nedjar-Kollim, B.; Bentarzi, Y.; Hammal, L.; Geronikaki, A.; Eleftheriou, P.; Lagunin, A., *Bioorg. Med. Chem.*, **2008**, *16 (6)*, 3059-3066; (b) Kolb, H. C.; Sharpless, K. B., *Drug Discovery Tooday*, **2003**, *8*, 1128-1137.

5. (a) Lei, M.; Zhan, Z.; Tian, W.; Ping Lu, P., *Tetrahedron*, **2012**, *68, (16)*, 3361-3367; (b) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith Karim, R. M.; Karim, A.; Gilmore, C. J.; Haltivanger, R. C.; Bryan, R. F., *J. Am. Chem. Soc.,* **1972**, *94 (4)*, 1354-1356.

6. Mosher, H. S.; Frankel, M. B.; Gregory, M., *J. Am. Chem. Soc*., **1953**, *75 (21)*, 5326-5328.
7. (a) Yang, J.; Hoffmeister, D.; Liu, L.; Fu, X.; Thorson, J. S., *Bioorg. Med. Chem.,* **2004**, *12 (7),* 1577-1584; (b) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. J., *J. Am. Chem. Soc.,* **2006**, *128 (5),* 1398-1399.
8. (a) Wu, P.; Feldmann, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V., *Angew. Chem. Int. Ed.*, **2004**, *43 (30)*, 3928-3932; (b) Helms, B.; Mynar, J. L.; Hawker, C. J.; Frechet, J. M. J., *J. Am. Chem. Soc.*, **2004**, *126 (46)*, 15020-15021; (c) Devadoss, A.; Chidsey, C. E. D., *J. Am. Chem. Soc.*, **2007**, *129 (17)*, 2370-5371; (d) Bock, V. D. Hiemstra, H.; Maarseveen, V., *Eur. J. Org. Chem.*, **2005**, *1*, 51-68.
9. Pierce, M. E.; Parsons, R. L.; Radesca, L. A.; Lo, Y. S.; Silvermon, S.; Moore, J. R.; Islam, Q.; Chaodhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. F.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J., *J. Org. Chem.,* **1998**, *63 (23),* 8536-8543.
10. (a) Finn, M. G.; Fokin, V. V., *Chem. Soc. Rev.*, **2010**, *39 (4)*, 1231-1232. (b) Meldal, M.; Tornoe, C. W., *Chem. Rev.,* **2008**, *108 (8),* 2952-3015 and references therein.
11. (a) Angell, Y. L.; Burgess, K., *Chem. Soc. Rev.,* **2007**, *36 (10),* 1674-1689; (b) Dedola, S.; Nepogodiev, S. A.; Field, R. A., *Org. Biomol. Chem.,* **2007**, *5 (5),* 1006-1017; (c) Fournier, D.; Hoogenboom, R.; Schubert, U. S., *Chem. Soc. Rev.,* **2007**, *36,* 1369; (d) Fokin, V. V.; Jia, G.; Sharpless, K. B. *PCT Int. Appl*. (2007) WO 2007041451 A2; (e) Diaz, D. D.; Finn, M. G.; Fokin, V. V. *PCT Int. Appl.* (2007) WO 2007027493 A2.
12. (a) Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P. H.; Torrens, A.; Yenes, S.; Pericas, M. A., *Org. Lett.,* **2008**, *10 (8),* 1617-1619; (b) Cantel, S.; Isaad, A. L. C.; Scrima, M.; Levy, J. J.; DiMarchi, R. D.; Rovero, P.; Halperin, J. A.; D'Ursi, A. M.; Papini, A. M.; Chorev, M., *J. Org. Chem.,* **2008**, *73 (15),* 5663-5674.
13. In a recent SciFinder search of the key phrase "azide-alkyne cycloaddition", more than 95 % of the 'hits' obtained were found to involve intermolecular version of the cycloaddition.
14. (a) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G., Angew. Chem. Int. Ed., 2005, 44 (15), 2215-2220; (b) Weller, R. L.; Rajski, S. R., Org. Lett., 2005, 7 (11), 2141-2144.
15. Huisgen, R., *Proceedings of the Chemical Society,* **1961**, 357-369.
16. (a) Meldal, M.; Tomoe, C. W., *Chem. Rev.,* **2008**, *108 (8),* 2952-3015; (b) Abood, N. A.; Schretzman, L. A.; Flynn, D. L.; Houseman, K. A.; Wittwer, A. J.; Dilworth, V. M.; Hippenmeyer, P. J.; Holwerda, B. C., *Bioorg. Med. Chem. Lett.,* **1997**, *7 (16),* 2105-2108.
17. (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Gia, G., *J. Am. Chem. Soc.,* **2005**, *127 (46),* 15998-15999; (b) Majireck, M. M.; Weinreb, S. M., *J. Org. Chem.,* **2006**, *71 (22),* 8680-8683; (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V., *J. Am. Chem. Soc.,* **2008**, *130 (28),* 8923-8930.
18. Ray, A.; Manoj, K.; Bhadbhade, M. M.; Mukhopadhyay, R.; Bhattacharjya, A., *Tetrahedron Lett.*, **2006**, *47 (16)*, 2775-2778.
19. (a) Mekni, N.; Baklouti, A., *Taibah International Chemistry Conference Marsh* **2009**, P 572; (b) Li, R.; Jansen, D. J.; Datta, A., *Org. Biomol. Chem.,* **2009**, *7 (9),* 1921-1930.
20. Kolb, H. C.; Sharpless, K. B., *Drug Discovery Today,* **2003**, *8 (24),* 1128-1137.
21. Krasinski, A.; Fokin, V. V.; Sharpless, K. B., *Org. Lett.,* **2004**, *6 (8),* 1237-1240.
22. Stephens, R. D.; Castro, C. E., *J. Org. Chem.*, **1963**, *28 (12),* 3313-3315.
23. Mekni, N.; Baklouti, A., *J. Soc. Chim. Tunisie*, **2009**, *11 (1)*, 15-20.
24. (a) Fujita, M.; Okubo, Y.; Sugimura, T., *Tetrahedron Lett*., **2009**, *50 (12)*, 1298-1300; (b) Cribiu, R.; Borbas, K. E.; Cumpstey, I., *Tetrahedron*, **2009**, *65 (10)*, 2022-2031.
25. (a) Blakemore, D. C.; Bryans, J. S.; Camell, P.; Carr, C. L.; Chessum, N. E. A.; Field, M. J. Kinsella, N.; Osbome. S. A.; Warren, A. N.; Williams, S. C., *Bioorg. Med. Chem. Lett.*, **2010**, *20 (2)*, 461-464; (b) Castillon, S.; Melendez; E.; Vilarrasa, J., *J. Heterocyclic Chem.*, **1982**, *19*, 61; (c) Driss, C.; Chaabouni, M. M.; Baklouti, A., *J. Fluorine Chem.*, **1994***, 67 (2)*, 137-141; (c) Baklouti, A.; Chaabouni, M. M., *J. Fluorine Chem.,* **1981**, *19 (2)*, 181-190; (d) Baklouti, A.; El Gharbi, R., *J. Fluorine Chem.,* **1979**, *13 (4)*, 297-314.
26. Mekni, N.; Hedhli, A.; Baklouti, A., *J. Fluorine Chem.*, **2002**, *114 (1)*, 43-46.
27. Mekni, N.; Baklouti, A., *J. Soc. Chim. Tunise*, **2005**, *7 (2)*, 205-207.