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## Synthesis of new triheterocyclic compounds, precursors of biheterocyclic aminoacids

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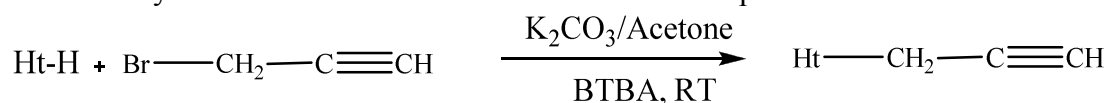
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**Abstract:** Heterocyclic alkynes **1-2** were obtained easily in good yield by N-alkylation of carbazole or benzimidazole with propargyl bromide. The 1,3-dipolar cycloaddition of these alkynes with the 4-azidomethyl-4-methyl-2-phenyloxazoline **3** afford new oxazolinic derivatives **4-5**, precursors of biheterocyclic aminoalcohols, aminoaldehydes and amino acids.

**Keywords:** N-alkylation, 1,3-dipolar cycloaddition, oxazolinic precursors, N-propargyl

The 1,3-dipolar cycloaddition reaction as a versatile method for preparing five-membered heterocyclic compounds is a classical reaction in organic chemistry and has been studied extensively. These cycloadditions have been utilized for the preparation of compounds that are of fundamental importance in diverse fields of chemistry [1-5]. Continuing our research [6] concerning heterocyclic  $\alpha$ -amino acids derivatives which present interesting biological activity [7] due to the presence of the heterocyclic cores as in the case of  $\beta$ -(1,2,4-triazol-1-yl)-L-alanine,  $\beta$ -pyrazolylalanine and L-trans-4-(1H-tetrazol-5-yl) proline, we described in this paper the preparation of new precursors of biheterocyclic amino acids. This approach consists of preparing firstly, heterocyclic dipolarophiles by nucleophilic substitution of propargyl bromide with carbazole or benzimidazole compounds. The 1,3-dipolar cycloaddition of these alkynes with the 4-azidomethyl-4-methyl-2-phenyloxazoline **3** afford new triheterocyclic compounds **4-5** (**a,b**) with good yields.

As shown in Scheme 1, the reaction of nitrogen heterocyclic derivatives (carbazole, or benzimidazole) with propargyl bromide and K<sub>2</sub>CO<sub>3</sub>, was carried out in the presence of a catalytic amount of tetrabutylammonium bromide in acetone at room temperature.



Ht-H = carbazole, benzimidazole  
TBAB : tetrabutylammonium bromide

**1** : Ht=carbazoyl  
**2** : Ht= benzimidazoyl

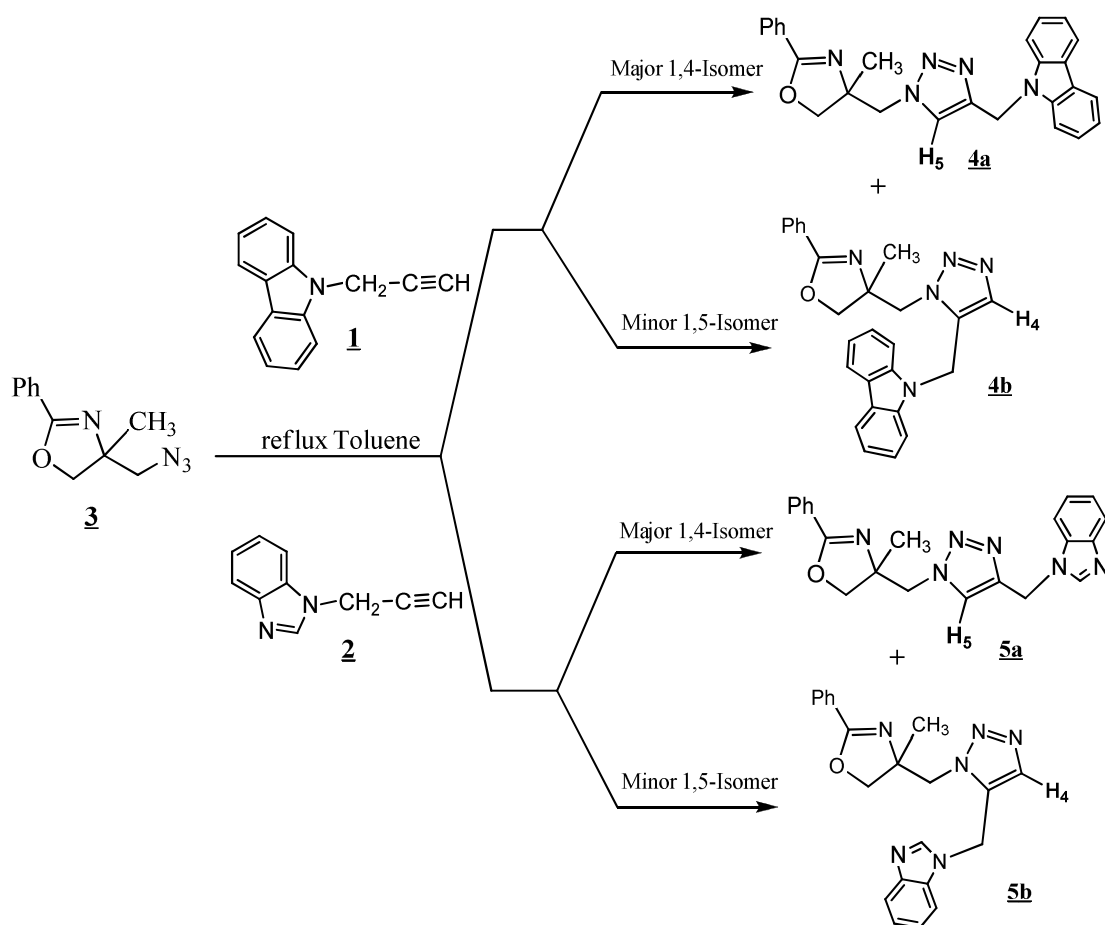
**Scheme 1**

The compounds **1**, **2** are stable and can be stored for unlimited time without any signs of decomposition. Products **1**, **2** were obtained in good yield and were characterized by MS,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy. The results are summarised in table I.

**TABLE I.** Synthesis of Heterocyclic Alkynes **1-2**

<i>Product</i>	<i>Ht-H</i>	<i>m.p.</i> (°C)	<i>Yield</i> (%)
<b>1</b>	Carbazole	107-109	78
<b>2</b>	Benzimidazole	< 40	87

The heterocyclic dipolarophiles **1**, **2** thus prepared were submitted to cycloaddition reaction with azide **3** (Scheme 2). 2-phenyl-4-methyl-4-(azidomethyl)oxazoline **3** was prepared in three steps from the commercially available 2-amino-2-methyl propan-1,3-diol using El Hajji's method [9a] . The results are summarised in table II :



**Scheme 2**

**TABLE II.** Synthesis of triheterocyclic derivatives **4-5 (a, b)**

<i>Product</i>	<i>Ht-H</i>	<i>m.p.</i> (°C)	<i>Yield (%)</i>	Ratio of isomers 1,4/1,5
<b>4a</b>	Carbazole	146-148	90	75
<b>4b</b>		208-210		25
<b>5a</b>	Benzimidazole	Orange oil	86	80
<b>5b</b>		152-154		20

The reaction of 1,3-dipolar cycloaddition is carried out with a good yield (86-90%). We isolated after column chromatography on silica gel two isomers during each reaction of cycloaddition. The products **4-5 (a,b)** were all characterized by MS, <sup>1</sup>H NMR, <sup>13</sup>C NMR spectroscopy.

The reaction of cycloaddition leads normally to the formation of two regioisomers (1,4-isomer and 1,5-isomer) with prevalence of the 1,4-isomer [8,9]. The structures of the two regioisomers **4-5 (a,b)** were assigned on the basis of literature data concerning the chemical shifts of triazolic protons [8,9] in positions 4 and 5. The studies carried out have shown that the triazolic proton signal for the 1,5-isomer lies downfield from the corresponding signal for the 1,4-isomer (Table III).

**TABLE III.** The chemical shifts of triazolic protons in <sup>1</sup>H NMR for 1,4 and 1,5 isomers.

<i>Ht</i>	<i>1,4-Isomer</i>	<i>1,5-Isomer</i>	<i><sup>1</sup>H NMR</i>	
			$\delta_{H_4}$ ppm	$\delta_{H_5}$ ppm
Carbazoyl	<b>4a</b>	-	-	7,28
	-	<b>4b</b>	7,1	-
Benzimidazoyl	<b>5a</b>	-	-	7,54
	-	<b>5b</b>	7,28	-

In conclusion, we elaborated an easy procedure for the preparation of triheterocyclic compounds on using an oxazoline as a masked amino acid. These products can be transformed into biheterocyclic aminoalcohols derivatives and they may be useful starting compounds for the preparation of new biheterocyclic amino acids.

### Acknowledgements

We thank the CNR for financial support of this work (PROTARS D13/03, Morocco).

### EXPERIMENTAL

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra (<sup>1</sup>H, <sup>13</sup>C) were recorded on a Bruker AM 300 (operating at 300.13 MHz for <sup>1</sup>H, at 75.47 MHz for <sup>13</sup>C) spectrometer (Centre Universitaire Régional d'Interface, Fès). NMR

data are listed in ppm and are reported relative to tetra-methylsilane ( $^1\text{H}$ ,  $^{13}\text{C}$ ); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualised under UV light or by exposure to vaporised iodine. Mass spectra were recorded on a PolarisQ Ion Trap GC/MSn Mass Spectrometer (Centre Universitaire Régional d'Interface, Fès). 4-azidomethyl-4-methyl-2-phenyloxazoline **3** was prepared in three steps from the commercially available 2-amino-2-methyl propan-1,3-diol using El Hajji's method [9a].

### Typical procedure for N-alkylation

To a stirred solution (10 mmols) of nitrogen heterocyclic compound, potassium carbonate (15 mmols) and a catalytic amount of tetrabutylammonium bromide in 10 ml of dry acetone, 10 mmols of propargyl bromide was added. The mixture was stirred at room temperature for 16 hours. The solvent was evaporated under vacuum and the residue was extracted with ether. The organic layer was dried with sodium sulfate ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed. The product was purified by column chromatography on silica gel using ether/hexane as eluant to afford the pure heterocyclic alkynes **1** and **2**.

*9-(prop-2-ynyl)-9H-carbazole 1*: Yield=78% (white solid); mp = 107-109°C; R<sub>f</sub> = 0.32 (hexane);  $^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.30 (t, 1H, J= 3Hz,  $-\text{C}\equiv\text{C}-\text{H}$ ); 5.05 (d, 2H, J= 3Hz,  $-\text{CH}_2-\text{C}\equiv\text{C}-$ ); 7.20-7.30 (m, 2H,  $\text{H}_{\text{carbazole}}$ ); 7.45-7.55 (m, 4H,  $\text{H}_{\text{carbazole}}$ ); 8.12 (d, 2H, J= 8Hz,  $\text{H}_{\text{carbazole}}$ ).  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ ): 32.33; 72.30; 77.91; 108.79; 119.65; 120.52; 123.33; 125.97; 139. MS(EI): m/z (%) : 205.1 (100)  $[\text{M}]^+$  [ $\text{C}_{15}\text{H}_{11}\text{N}$ ]

*1-(prop-2-ynyl)-1H-benzimidazole 2*: Yield=87% (white solid); mp = < 40°C, R<sub>f</sub> = 0.36(ether/hexane 1:1).  $^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.51 (t, 1H, J= 2.6 Hz,  $-\text{C}\equiv\text{C}-\text{H}$ ); 4.92(d, 2H, J= 2.6Hz,  $-\text{CH}_2-\text{C}\equiv\text{C}-$ ); 7.28-7.84(m, 4H,  $\text{H}_{\text{arom}}$ ); 8.04(s, 1H,  $\text{H}_{\text{imidazol}}^2$ ).  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm : 34.63; 74.97; 76.01; 109.7; 120.49; 122.62; 123.32; 133.32 142.26; 143.76. MS(EI): m/z (%) 156.1 (100)  $[\text{M}]^+$  [ $\text{C}_{10}\text{H}_8\text{N}_2$ ]

### Cycloaddition reaction: general procedure

The azide **3** and the dipolarophile (**1** or **2**) were magnetically stirred in a minimum volume of toluene at reflux for 72 hours. After evaporation of the solvent, the residue was chromatography over silica gel to give our products.

*4-((4-((9H-carbazol-9-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-4-methyl-2-phenyl-4,5-dihydrooxazole 4a*: (white solid); mp= 146-148°C; R<sub>f</sub> = 0.25(ether).

$^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm : 1.41(s, 3H); 4.01, 4.49 (AB, 2H, J= 9Hz); 4.35, 4.46 (AB, 2H, J= 14Hz); 5.45, 5.57 (AB, 2H, J= 16,8Hz); 7.19-7.50 (m, 9H,  $\text{H}_{\text{arom}}$ ), 7.28 (1H, s,  $\text{H}_{1,2,3\text{-triazole}}^5$ ); 7.69-8.07 (m, 4H,  $\text{H}_{\text{arom}}$ ).

$^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 24.87; 37.98; 57.08; 70.80; 75.18; 109.96; 119.41; 120.64; 122.66; 124.89; 126.12; 127.46; 128.34; 129.03; 132.17; 140.22; 143.32; 162.97. MS(EI):  $m/z$  (%) 421.1 (63)  $[\text{M}]^+$   $[\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}]$ ; 160.1 (100).

Anal. calcd. for  $\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}$  (421): C 74.10; H 5.46; N 16.62; Found: C 73.84; H 5.14; N 16.38.

4-[(5-((9H-carbazol-9-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl]-4-methyl-2-phenyl-4,5-dihydrooxazole **4b**: (white solid); mp= 208-210°C;  $R_f$  = 0.35(ether).

$^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 1.57(s, 3H); 4.24, 4.83 (AB, 2H,  $J$  = 9Hz); 4.52, 4.58 (AB, 2H,  $J$  = 14,4Hz); 5.58, 5.88 (AB, 2H,  $J$  = 17Hz); 7.1 (s, 1H,  $\text{H}^4_{1,2,3\text{-triazole}}$ ), 7.25-7.6 (m, 9H,  $\text{H}_{\text{arom}}$ ); 7.98-8.11(m, 4H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.61; 37.64; 55.56; 71.60; 75.05; 108.88; 119.78; 120.64; 123.24; 126.03; 128.32; 128.56; 128.77; 132.27; 133.46; 134.64; 140.20; 162.68. MS(EI):  $m/z$  (%) 421.1 (97)  $[\text{M}]^+$   $[\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}]$ ; 105.1 (100).

Anal. calcd. for  $\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}$  (421): C 74.10; H 5.46; N 16.62; Found: C 74.14; H 5.38; N 16.65.

4-[(4-((1H-benzimidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl]-4-methyl-2-phenyl-4,5-dihydrooxazole **5a**: (orange oil);  $R_f$  = 0.15(ether/hexane 3/2).

$^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ ): 1.41(s, 3H); 4.07, 4.42 (AB, 2H,  $J$  = 9Hz); 4.41, 4.51 (AB, 2H,  $J$  = 14Hz); 5.34, 5.42 (AB, 2H,  $J$  = 15,8Hz); 7.18-7.51(m, 6H,  $\text{H}_{\text{arom}}$ );

7.54 (s, 1H,  $\text{H}^5_{1,2,3\text{-triazole}}$ ); 7.73-7.78 (m, 3H,  $\text{H}_{\text{arom}}$ ), 8.01 (s, 1H,  $\text{H}^2_{\text{imidazole}}$ ).

$^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ ): 24.83; 40.60; 57.79; 70.53; 74.68; 109.95; 119.94; 122.71; 123.47; 123.82; 126.74; 128.13; 128.53; 131.94; 133.19; 142.40; 142.57; 142.57; 164.51.

MS(EI):  $m/z$  (%) 372.2 (20)  $[\text{M}]^+$   $[\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}]$ ; 157.1 (100).

4-[(5-((1H-benzimidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl]-4-methyl-2-phenyl-4,5-dihydrooxazole **5b**: (white solid); mp= 152-154°C;  $R_f$  = 0.32(ether/hexane 3:2).

$^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 1.51(s, 3H); 4.20, 4.67 (AB, 2H,  $J$  = 9Hz); 4.35, 4.52 (AB, 2H,  $J$  = 14,4Hz); 5.63, 5.83 (AB, 2H,  $J$  = 16,6Hz); 7.06-7.25 (m, 2H,  $\text{H}_{\text{arom}}$ ), 7.28 (s, 1H,  $\text{H}^4_{1,2,3\text{-triazole}}$ ), 7.30-7.35 (m, 1H,  $\text{H}_{\text{arom}}$ ), 7.41-7.49 (m, 2H,  $\text{H}_{\text{arom}}$ ); 7.53-7.56 (m, 1H,  $\text{H}_{\text{arom}}$ ); 7.81-7.91 (m, 3H,  $\text{H}_{\text{arom}}$ ); 8.1(s, 1H,  $\text{H}^2_{\text{imidazole}}$ ).  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.4; 39.17; 55.94; 71.72; 74.84; 109.87; 120.10; 123.29; 123.99; 126.74; 128.26; 128.78; 132.21; 133.11; 133.40; 136.14; 142.61; 142.61; 164.11.

MS(EI):  $m/z$  (%) 372.2 (33)  $[\text{M}]^+$   $[\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}]$ ; 105.0 (100).

Anal. calcd. for  $\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}$  (372): C 67.74; H 5.37; N 22.58; Found: C 67.91; H 5.29; N 22.83.

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