COPPER CATALYSED AZIDE-ALKyne CYCLOADDITION INVOLVING 1,12-DIAZIDODODECANE AND 1,5-BENZODIAZEPINE-2,4-DIONe DERIVATIVES

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Abstract : Copper catalysed azide-alkyne cycloaddition have been undertaken involving as azide 1,12-diazo-dodecane and 1,5-dibenzy1-3-propargyl-1,5-benzodiazepine-2,4-dione \textsuperscript{1} and 7-chloro-1,5-dipropargyl-1,5-benzodiazepine-2,4-dione \textsuperscript{2} as dipolarophiles. The reactions studied led exclusively in each case to 3-(1-azidododecyl-1,2,3-triazol-4-ylmethyl)-1,5-benzodiazepine-2,4-dione \textsuperscript{3} and a di-1,2,3-triazolyl macrocyclic ligand \textsuperscript{4}. The structures of compounds isolated \textsuperscript{3} and \textsuperscript{4} have been elucidated on the basis of \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and confirmed by a single crystal X-ray diffraction studies.

Keywords 1,5-benzodiazepine-2,4-dione, Copper catalysed azide-alkyne cycloaddition NMR and X-ray diffraction

Introduction
The chemistry of 1,5-benzodiazepine (BZDs) derivatives was intensely developed due to their biological activities [1-4]. BZDs can be used as inhibitors of reverse transcriptase of HIV-I virus, antiarrhythmic agents, ligands of benzodiazepine receptors in GABAergic system and cholecystokinin receptor antagonists [5]. Moreover, 1,5-benzodiazepine acafeold constitutes an highly efficient pharmacophore existing in a wide variety of bioactive heterocyclic compounds. They are used in medicinal chemistry
as an anxiolytic agents such as clobazam which is also used as an adjunctive treatment for difficult to treat seizures [6].

In continuation of our previous research works on 1,5-benzodiazepine-2,4-diones [7-20], we report in this article the Copper catalyzed azide-alkyne cycloadditions (CuAAC) involving 1,5-dibenzyl-3-propargyl-1,5-benzodiazepine-2,4-dione 1 and 7-chloro-1,5-dipropargyl-1,5-benzodiazepine-2,4-dione 2 as dipolarophiles and 1,12-diazido-dodecane as dipole in the mixture of t-butylalcohol/water in the presence of copper sulfate pentahydrate and sodium ascorbate for 12 hours. In all cases we have obtained exclusively the 1,4-disubstituted-1,2,3-triazole regioisomers 3 and 4 (scheme 1)

![Scheme 1](image)

1- \( R_1 = H; \ R_2 = -\text{CH}_2\text{Ph}; \ R_3 = -\text{C}_3\text{H}_3 \)
2- \( R_1 = \text{Cl}; \ R_2 = -\text{C}_3\text{H}_3; \ R_3 = H \)

These results are similar to those previously observed by Sebbar et al [20] and Ellouz et al. [21], when they studied Copper catalyzed azide-alkyne cycloaddition reactions involving propargyl-1,4-benzothiazin-3-one derivatives as dipolarophiles.
The structures of the two compounds 3 and 4 isolated have been elucidated using spectral data ($^1$H NMR, $^{13}$C NMR) and confirmed by a single-crystal X-ray diffraction studies. The $^1$H NMR spectrum of compound 3 shows in particular the presence of a signal at 7.48 ppm corresponding to the 1,2,3-triazolic proton, as well as a triplet assigned to the methylene group at 4.27 ppm.

The crystallographic study of compound 3 shows that the membered ring adopts a boat conformation with the azidododecyl-1,2,3-triazolyl bearing C-atoms as the prow and the fused-ring C atoms as the stern. Moreover, the azidododecyl-1,2,3-triazolylmethyl substituent occupies an axial position. (Figure1, Table1)

Figure 1: Ortep diagram with numbering of 3-(1-azidododecyl-1,2,3-triazol-4-yl)methyl-1,5 dibenzyl-1,5-benzodiazepine-2,4-dione: 3
Crystal and refinement details are presented in table1

Table1 : Experimental details of compound: 3

Crystal data

C_{38}H_{46}N_{8}O_{2} \quad Z = 2
M_r = 646.83 \quad F(000) = 692
Triclinic, \textit{PT} \quad D_x = 1.214 \text{ Mg m}^{-3}
Hall symbol: -P 1 \quad \text{Mo K\textalpha\ radiation, } \lambda = 0.71073 \text{ Å}
\begin{align*}
a &= 9.4269 (2) \text{ Å} \\
b &= 12.3304 (3) \text{ Å} \\
c &= 15.5500 (4) \text{ Å} \\
\alpha &= 101.12 (2) ^\circ \\
\beta &= 92.17 (2) ^\circ \\
\gamma &= 92.93 (2) ^\circ \\
V &= 1769.11 (7) \text{ Å}^3
\end{align*}

Cell parameters from 3120 reflections
0 = 2.3-22.9°
\mu = 0.08 \text{ mm}^{-1}
T = 193 K
Plate: colorless
0.40 \times 0.20 \times 0.06 \text{ mm}

Data collection

Bruker APEXII
diffra tometer
Radiation source: fine-focus sealed tube
graphite
\varphi \text{ and } \omega \text{ scans}
33681 measured reflections
8126 independent reflections
4315 reflections with \( I > 2 \sigma(I) \)

Refinement

Refinement on \( R^2 \)
Least-squares matrix: full
\begin{align*}
R[F^2 > 2\sigma(F^2)] &= 0.052 \\
\omega R_F^2 &= 0.147 \\
S &= 1.00
\end{align*}

8126 reflections
433 parameters
\nu = 1.00

Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
\begin{align*}
\omega = & 1/[\sigma^2(F_o^2) + (0.0637P)^2 + 0.0087P] \\
\text{where } P = & (F_o^2 + 2F_c^2)/3 \\
(\Delta\sigma/\sigma)_{\text{max}} &= 0.001 \\
\Delta \rho_{\text{max}} &= 0.21 \text{ e Å}^{-3} \\
\Delta \rho_{\text{min}} &= -0.22 \text{ e Å}^{-3}
\end{align*}
The $^1$HNMR spectrum of compound 4 highlights in particular two signals at 7.70 and 7.72 ppm corresponding to the 1,2,3-triazolic protons as well as two triplets assigned to the methylene groups linked to the nitrogen atom of the 1,2,3-triazole nucleus.

The ditriazolo macrocyclic compound 4 with formula C$_{27}$H$_{35}$ClN$_8$O$_2$ crystallizes in triclinic space group P-1. The ORTP and the crystallographic data are given in figure 2 and table 2.

**Figure 2**: Ortep diagram with numbering of (7-chloro-2,4-dioxo-1,5-(1,2,3-triazol-4-yl)-methyl-1,5-benzodiazepino-25-crown 4

**Crystal and refinement details are presented in table2**

**Table2**: Experimental details of compound 4

<table>
<thead>
<tr>
<th></th>
<th>C$<em>{27}$H$</em>{35}$ClN$_8$O$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formule empirique</td>
<td></td>
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<tr>
<td>Masse moléculaire</td>
<td>539.08</td>
</tr>
<tr>
<td>Couleur du cristal, forme</td>
<td>Incolore, Bloc</td>
</tr>
<tr>
<td>Système cristallin</td>
<td>Triclinique</td>
</tr>
<tr>
<td>Groupe spatial</td>
<td>P-1</td>
</tr>
<tr>
<td>Dimensions de la cellule unité</td>
<td></td>
</tr>
<tr>
<td>a(A)</td>
<td>10.1524(3)</td>
</tr>
<tr>
<td>b(A)</td>
<td>11.9648(4)</td>
</tr>
<tr>
<td>c(A)</td>
<td>13.7747(5)</td>
</tr>
<tr>
<td>$\alpha$(deg)</td>
<td>93.151(3)</td>
</tr>
<tr>
<td>β(deg)</td>
<td>111.385(2)</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>γ(deg)</td>
<td>114.829(2)</td>
</tr>
<tr>
<td>Volume (Å³)</td>
<td>1370.48(8)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Densité (g/cm³)</td>
<td>1.306</td>
</tr>
<tr>
<td>Coefficient d’absorption μ (mm⁻¹)</td>
<td>0.180</td>
</tr>
<tr>
<td>F (000)</td>
<td>572</td>
</tr>
<tr>
<td>Taille du cristal (mm³)</td>
<td>0.24 x 0.18 x 0.10</td>
</tr>
<tr>
<td>Température (K)</td>
<td>193(2)</td>
</tr>
<tr>
<td>détecteur</td>
<td>Bruker SMART CCD</td>
</tr>
<tr>
<td>Données collectées de l’angle thêta (deg)</td>
<td>5.11 to 24.71</td>
</tr>
<tr>
<td>Reflétions collectées</td>
<td>24390</td>
</tr>
<tr>
<td>R(int)</td>
<td>0.0382</td>
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<tr>
<td>Méthode d’affinement</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Données /contrainte /paramètres</td>
<td>4615 / 64 / 426</td>
</tr>
<tr>
<td>R indices [I&gt;2sigma(I)]ᵃ</td>
<td>R₁ = 0.0559, wR₂ = 0.1182</td>
</tr>
<tr>
<td>R indices (all data)ᵃ</td>
<td>R₁ = 0.0709, wR₂ = 0.1245</td>
</tr>
<tr>
<td>Max. diff de pointe et trou (e/Å³)</td>
<td>0.324, -0.241</td>
</tr>
</tbody>
</table>

**Conclusion**

In this work we studied the Copper catalysed azide-alkyne cycloaddition (click chemistry) between propargylated 1,5-benzodiazepine-2,4-dione derivatives and 1,12-diazido-dodecane. We isolated exclusively in each case a novel 1,4-disubstituted-1,2,3-triazolic regioisomers 3 and 4. The structures of the two cycloadducts were elucidated on the basis of spectral data (¹HNMR, ¹³CNMR), and confirmed by a single-crystal X-ray diffraction studies.

**Experimental**

**Materials and physical instruments**

In this strategy procedure, all the chemical reagents were purchased from Fluka Analytical Merck company and the melting points were taken in capillary tube on a electrothermal...
standard digital melting point apparatus 120 VAC. Analyses were performed with $^1$H NMR (300 MHz) and $^{13}$C NMR, a spectra were recorded $d_6$-DMSO on a Bruker AC-300 Avance spectrometer, using tetramethylsilane (TMS) as an internal standard. Crystallographic data and structure refinement details were taken by The PAN alytical X’Pert PRO.

**12-azido-[4'(1,5-dibenzyl-1,5-benzodiazépine-2,4-dione)méthyl]-1',2',3'-triazolyl-4'-yl) dodecane : 3**

**General strategy and procedure for the synthesis of the compounds studied.**

Synthesis of compound: 3

To a solution of 0.2 g (5.07 $10^{-4}$ mol) of 1,5-dibenzyl-3-propargyl-1,5-benzodiazepin e-2,4-dione 1 in ethanol/water : 1/2 (8ml) were added 1.2 eq of 1,12-diazidododecane (5mmol), copper sulfate pentahydrate (1mmol) and sodium ascorbate (2 mmol). The reaction mixture was stirred for 24h. The solution was diluted with 20 ml of water. The organic compound was extracted with 2x20 ml of ethyl acetate. The extracts were washed with brine, dried over sodium sulfate. After decantation and concentration under reduced pressure of the organic phase, the residue obtained was recrystallized from ethyl acetate/ether to afford colorless crystals.

Yield : 72 %, m.p : 110-112 ºC ; fr: 0.58 (ethyl acetate /hexane-1/2) ; NMR $^1$H (CDCl$_3$) δ ppm: 1.28, 1.62, 1.89 (3m, 20H, CH$_2$-C), 3.26 (t, 2H, CH$_2$-C=C), 3.47 (d, 2H, CH$_2$-C), 4.27 (t, H, CO-CH), 5.00 (sytème AB, 4H, CH$_2$N), 7.04-7.29 (m,14H, CHarom), 7.48 (s, H, CH triazolic). NMR $^{13}$C (CDCl$_3$) δ ppm: 166.45 (2C=O); 145.06 (C=C, Cq triazolic); 136.87; 135.58 (CHarom, Cq); 122.38 (C=C, Ct triazolic); 128.66, 127.35, 126.92, 126.88, 123.35 (CHarom , Ct), 51.90 (-CH$_2$-N), 51.49 ( -CH$_2$-N$_3$), 50.21(CH-CO); 49.22 (CH$_2$-N); 30.29, 29.45, 29.36, 29.14, 29.01, 28.84, 26.71 ( C-CH$_2$-C); 23.01 (CH$_2$-C=C).

Synthesis of compound: 4

To a solution of 0.15g (5.2 $10^{-4}$ mol) of 7-chloro-1,5-dipropargyl-1,5-benzodiazépine-2,4-dione 2, 1.2 eq (0.15g; 6.24 $10^{-4}$mol) of 1,12-diazido-dodecane in 7ml of ethanol/water : 1/2 were added 1 eq of copper sulfate pentahydrate (0.08g ; 5.2 $10^{-4}$mol) and 2eq of sodium ascorbate (0.2g ; 1.04 $10^{-3}$mol) dissolved in 7ml of distilled water. The reaction mixture was stirred at room temperature for 24h. The progress of the reaction was monitored by thin layer chromatography. The solution was filtered and concentrated in reduced pressure. The residue obtained was purified by column chromatography on silica gel.

**7-Chloro-2,4-dioxo-1,5-di[(1’,2’,3’-triazol-4’-yl)-méthyl]-1,5-benzodiazépino-25 crown : 4**

Yield : 40 %, m.p :137-139 ºC ; fr = 0.91 (ethyl acetate) ; NMR $^1$H (CDCl$_3$) δ ppm: 1.13-1.46 (m, 20 H, 10 CH$_2$(aliphatic)); 3.29 (d, H$_B$, CH$_2$=C=O, J$_{AB}$=12.5 Hz); 3.43 (d, H$_A$, CH$_2$=C=O, J$_{AB}$=12.5 Hz); 4.23-4.65 (2t, 4H, 2 CH$_2$-Ntriazolic, J=7 Hz); 5.02 (s, 4H, CH$_2$-N diazeinic); 7.5 (dd, 1H, Harom en position 8, $^3$J=8.83 Hz, 4J=2.38 Hz ); 7.69 (d, 1H, Harom en position 9, $^3$J=8.83 Hz); 7.74 (d, 1H, Harom en position 6, $^4$J=2.38 Hz); 7.70-7.72 (2 s, 2 H, 2 CH-triazolic ; NMR $^{13}$C(CDCl$_3$) δ ppm:165.41-165.37(2C=O); 147.23-149.89 Cq triazolic); (137.17 (Cq-arom en position 5’); 134.83 (Cq-arom at position 9’); 131.66 (Cq-arom at position 7); 126.45 (CH-arom at position 8); 123.85 (CH-arom en position 9); 122.71 (CH-arom en position 6); 62.02-62.56(2 CH$_2$-Ntriazolic); 50.32-50.29 (2 CH$_2$-N-diazepinic); 44.25 (CH$_2$-CO) ; 26.12-19.82 (10 CH$_2$(aliphatic).
References

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