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Intramolecular copper(I)-catalyzed 1,3-dipolar cycloaddition of azido-alkynes: synthesis of triazolo-benzoxazepine derivatives and their biological evaluation

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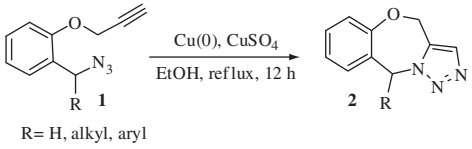
ABSTRACT

Synthesis of a series of [1,2,3] triazolo [5,1-*c*] [1,4]benzoxazepine derivatives have been accomplished by the intramolecular Cu(I)-catalyzed cycloaddition of azido-alkynes derived from salicylaldehyde. The biological profile of these heterocyclic structural scaffolds toward anti-bacterial as well as anti-fungal activity has also been illustrated.

The synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition of azides with alkynes was discovered by Arthur Michael at the end of the 19th century and significantly developed by Rolf Huisgen in 1960s.[1] In early 2002, Meldal and Sharpless research groups independently reported the use of catalytic amount of Cu(I)-catalyst in the regioselective cycloaddition of azide and alkynes.[2] After this discovery, in the past decade the Cu-catalyzed [3+2] cycloaddition reaction between alkynes and azides has gained considerable attention as 'click chemistry', which has resulted in a variety of applications in synthetic organic chemistry,[3] material science,[4] drug discovery,[5] polymer chemistry[6] and bio-conjugation,[7] among others.[8] The 1,3-dipolar cycloaddition reaction has also been used for the construction of various novel 1,2,3 triazolo heterocyclic compounds.[9] These cycloaddition reactions have been accomplished either in intermolecular or intramolecular version.[10,11] The intramolecular click reaction provides fused triazoles, which are endowed with a wide range of biological activities.[4b,12] Hence, in continuation to our ongoing research on 'click chemistry',[13] we were interested in exploring the cycloaddition reaction in an intramolecular fashion for the formation of triazolo-benzoxazepine derivatives[14] (Scheme 1).

Starting from salicylaldehyde, the desired azido-alkyne **1** was prepared in three-steps as shown in Scheme 2. In the first case, salicylaldehyde (**3**) was alkylated with propargyl bromide in the presence of K_2CO_3 in acetone under refluxing conditions to obtain the *O*-propargylated aldehyde **4**,[15] in 92% yield. The reaction of **4** with phenyl magnesium bromide in dry diethyl ether at room temperature provided the alcohol **5a** in 89% yield. To install the azide functionality, the alcohol **5a** was treated with $TMSN_3$ in the presence of BF_3Et_2O (20 mol %) in CH_2Cl_2 at room temperature, which provided the azido-alkyne **1a** (98%). Having the azido-alkyne **1a** in hand, the intramolecular Cu(I)-catalyzed cycloaddition reaction was carried out for the synthesis of triazolo-[1,2,3]-benzoxazepine derivative **2a**.[16] Thus, the azido-alkyne **1a** was treated with copper(I)-catalyst in ethanol under refluxing conditions to afford the triazolo-[1,2,3]-benzoxazepine **2a** in 84% yield via intramolecular 1,3-dipolar cycloaddition reaction. The structure of compound **2a** was determined by X-ray crystallographic studies[17] (Fig. 1) and fully characterized by its spectral analysis.[18]



Scheme 1. Intramolecular 1,3-dipolar cycloaddition.

With this success in the preparation of a novel heterocyclic scaffold, we were encouraged to prepare various substituted fused

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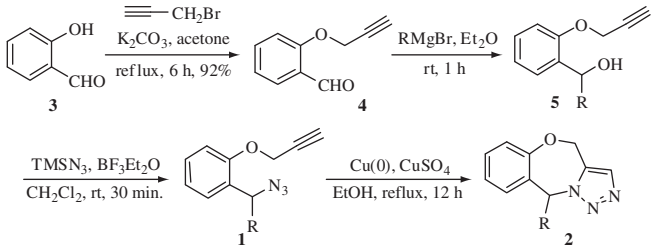


R	yield of **5** (%)[a]	yield of **1** (%)[b]	yield of **2** (%)[c]
Phenyl	**5a**, 89%	**1a**, 98%	**2a**, 84%
2-Naphthyl	**5b**, 86%	**1b**, 96%	**2b**, 83%
4-Methoxyphenyl	**5c**, 89%	**1c**, 94%	**2c**, 85%
(3,5-Dioxomethylene)phenyl	**5d**, 88%	**1d**, 97%	**2d**, 82%
4-Methylphenyl	**5e**, 89%	**1e**, 93%	**2e**, 81%
Benzyl	**5f**, 87%	**1f**, 92%	**2f**, 79%
Allyl	**5g**, 89%	**1g**, 95%	**2g**, 81%
n-Pentyl	**5h**, 90%	**1h**, 94%	**2h**, 83%
n-Octyl	**5i**, 88%	**1i**, 93%	**2i**, 80%
Hexynyl	**5j**, 86%	**1j**, 92%	**2j**, 78%

[a]Isolated yield based on **4**; [b]Isolated yield based on **5**
[c]Isolated yield based on azido-alkyne **1**

Scheme 2. Synthesis of [1,2,3] triazolo [5,1-*c*] [1,4] benzoxazepines.

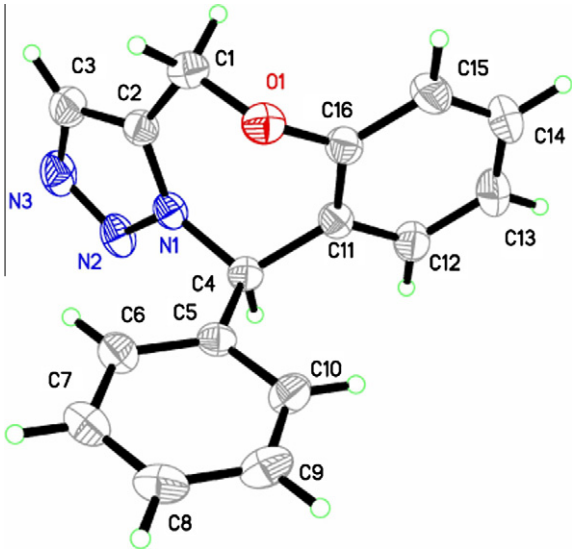
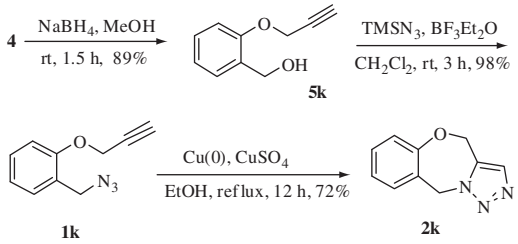


Figure 1. X-ray crystal structure of **2a**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

triazolo-[1,2,3]-benzoxazepine derivatives. As summarized in a table shown in Scheme 2, various azido-alkynes **1b–j** have been prepared from *O*-propargylated aldehyde **4** following a similar two-step sequence used for **1a**; (i) reaction of **4** with Grignard reagents to alcohols **5b–j**, (ii) conversion of alcohols **5b–j** to the corresponding azides **1b–j**. All the prepared azido-alkynes **1b–j** were subjected to Cu(I)-catalyzed intramolecular 1,3-dipolar cycloaddition reaction to afford the corresponding substituted triazolo-benzoxazepine derivatives **2b–j** in good yields. It is obvious that a wide variety of aryl (**1a–e**), benzyl (**1f**), allyl (**1g**), alkyl (**1h–i**) and alkynyl (**1j**) substituted azido-alkynes successfully participated in the intramolecular cycloaddition reaction.[19]



Scheme 3. Synthesis of **2k** from salicylaldehyde.

Finally, unsubstituted triazolo-benzoxazepine derivative **2k** was also prepared in a three-step sequence, where the aldehyde **4** was reduced ($NaBH_4$/MeOH) to the primary alcohol **5k** followed by azide formation ($TMSN_3/BF_3{\cdot}Et_2O$) and 1,3-dipolar cycloaddition under the optimized reaction conditions (Scheme 3).

Further, the biological profile of the above prepared fused [1,2,3] triazolo [5,1-*c*] [1,4] benzoxazepines has been evaluated for anti-bacterial and anti-fungal activities. All the derivatives **2a–k** were tested using the microtiter broth dilution method for in vitro antimicrobial studies[20] and found that four compounds **2g–j** were moderately active. However, one of the derivatives **2h** was found to be promising and showed the lowest MIC value of 93.75 μg/ml against both Gram-positive and Gram-negative bacteria like *Staphylococcus aureus, Escherichia coli*, *Klebsiella planticola* and also against *Candida albicans*, suggesting the broad spectrum nature of the antimicrobial activity.

In conclusion, we have successfully employed an intramolecular click chemistry of azido-alkynes to generate fused [1,2,3] triazolo [5,1-*c*] [1,4] benzoxazepine derivatives. Additionally, the preliminary screening of the compounds obtained was carried out for antimicrobial activity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.040.

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16. The reaction was also tested in the absence of copper-catalyst (refluxing in ethanol), which did not proceed to provide any product.
17. CCDC 783658 contains the supplementary crystallographic data for the structure of **2a**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/datarequest/cif. Crystal data for compound **2a**: $C_{16}H_{13}N_3O$, $M = 263.29$, orthorhombic, space group $P2_12_12_1$, $a = 8.1550(5)$Å, $b = 9.8788(6)$Å, $c = 16.8120(11)$Å, $V = 1354.40(15)$Å^3, $Z = 4$, $D_{calcd} = 1.291$ mg m^{-3}, $T = 294(2)$K, $\mu = 0.084$ mm^{-1}, $F(0\,0\,0) = 552$, $\lambda = 0.71073$Å. Data collection yielded 13022 reflections resulting in 1398 unique, averaged reflection, 1351 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final $R = 0.0271$, $wR = 0.0742$ and GOF = 1.151. Intensity data were measured on Bruker Smart Apex with CCD area detector.
18. *10-Phenyl-4,10-dihydrobenzo[f][1,2,3]triazolo[5,1-c] [1,4] oxazepine* (**2a**): White solid; mp 134–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.37 (m, 2H) 7.30–7.24 (m, 4H), 7.23–7.07 (m, 2H), 6.95–6.90 (m, 3H), 5.28 (d, 1H, $J = 15.1$ Hz), 5.03 (d, 1H, $J = 15.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 139.5, 130.9 (2C), 128.6 (3C), 128.0, 126.7, 125.9 (3C), 124.1, 122.3, 66.7, 63.4; IR (KBr): ν 3423, 2925, 1782, 1489, 1196, 1027, 739 cm^{-1}; MS (ESI): 264 $[M+H]^+$; HRMS (ESI): Calcd for $C_{16}H_{14}N_3O$: 264.1131 $[M+H]^+$; found 264.1137 $[M+H]^+$.
19. *General experimental procedure for Cu(I)-catalyzed cycloaddition of azido-alkynes*: To a stirred solution of azido-alkyne **1a**–**k** (0.38 mmol) in EtOH (10 mL) was added saturated copper sulfate solution (0.2 mL, 1 M), Cu-turnings (20 mg) and the reaction mixture was refluxed for 12 h. After completion of the reaction (monitored by TLC), the mixture was filtered through celite. The celite pad was washed with ethyl acetate and the combined organic volatiles were removed on a rotary evaporator. The residue was purified by column chromatography over silica gel with ethyl acetate/hexanes (3:7) as eluent to furnish the corresponding [1,2,3] triazolo [5,1-c] [1,4] benzoxazepines, **2a**–**k**.
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