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Report

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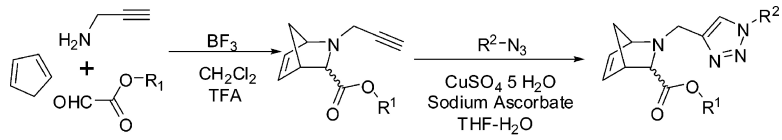

R^1 = Me, ^{t}Bu, Cy, R^2 = Bn, CH2-COOEt, CH2-S-Ph

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Click Chemistry Approach to Assembly Proline Mimetic Libraries Containing 1,4-Substituted 1,2,3-Triazoles

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The development of new therapeutic agents, as well as the identification of molecular probes for the study of the chemical/biological interfaces, is one of the major goals in biomedical research. In this context, the availability of large libraries of small organic molecules, covering as much chemical space as possible, is seen as the only means which guarantees potential modulation of the many biological targets that are ultimately being unveiled by genomics.[1] Therefore, advances in drug discovery depend heavily on the availability of synthetic transformations that allow the rapid assembly of complex molecular frameworks providing maximum diversity.

In this challenging scenario, cycloadditions[2] occupy an outstanding position because of their versatility, exploratory power, high degree of atom economy, and ability to generate small highly polyfunctionalized molecular skeletons. Within the diverse transformations comprising cycloadditions, aza-Diels−Alder reactions have attracted much interest, especially in those employing cyclopentadiene as starting material.[3] On the other hand, not only the enormous potential of 2-azabicyclo[2.2.1]hept-5-enes as synthetic precursors of diverse valuable structures[4] but also the growing biomedical interest in this template[5] because of its easse of origination of proline mimetic structures has stimulated continuous advances in the development of synthetic methods[6] able to produce functionally and stereochemically diverse 2-azabicyclo[2.2.1]hept-5-ene derivatives. Nevertheless, there is an increasing need for simple and efficient procedures that allow to incorporate unexplored diversity patterns in the bicyclic scaffold and simultaneously facilitate the assembly of more complex structures (e.g., by linking the 2-azabicyclo[2.2.1]hept-5-ene system to other well documented privileged druglike molecules or natural products).

In the context of our ongoing efforts toward the development of new methodologies to access structurally diverse heterocyclic libraries,[7] we report herein the facile assembly of a library of 2-azabicyclo[2,2,1]hept-5-enes incorporating, at position 2 of the bicyclic skeleton, a 1,2,3-triazole nucleus linked through alkyl chains of variable lengths distances (Figure 1). The proposed synthetic pathway is based on the combination of two highly versatile transformations: the aza-Diels−Alder reaction and the Cu^{I}-catalyzed Huisgen cycloaddition (Figure 1). The libraries are not only novel but also exemplify a simple and highly efficient assembly of pharmacologically valuable triazole containing proline mimetic structures.

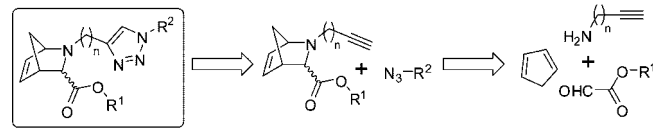

Figure 1. General structure of targeted libraries and retrosynthetic scheme.

The general structure of the targeted library, as well as the retrosynthetic analysis are presented in Figure 1. It should be pointed out that although Figure 1 discloses structures incorporating different alkylic linkages ($n = 1$, 2, or 3) between the privileged scaffolds, in this preliminary communication, we only describe the results obtained during the proof of the concept of the pathway, for example, using propargylamine as nitrogenated component ($n = 1$).

The feasibility of the proposed sequence relied on the successful preparation of the 2-azabicyclo[2.2.1]hept-5-ene template incorporating a reactive terminal acetylenic moiety at position 2. Thus, we proceeded to study the aza-Diels−Alder reaction of cyclopentadiene with a subset of glyoxylates **1a**−**c** (or their synthetic equivalents, e.g., hemiacetals or hydrates) having different alkyl residues in the ester moiety [e.g., Me, *t*-Bu, Cy (Cy = cyclohexyl)] and employing propargylamine as the amine component (Scheme 1). The three-component reaction that takes place in a consecutive manner is highly accelerated by the addition of a Lewis acid (e.g., boron trifluoride). The transformation starts with the in situ generation of a highly reactive aza-dienophile (iminium cation)[3] which rapidly undergoes a [4 + 2] cycloaddition under mild conditions to afford the desired (±) 2-propargyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**2a**−**e**) as variable endo/exo mixtures that were chromatographically separated under standard conditions.[8,9] Table 1 shows the isolated yield for all the six 2-azabicycloalkene adducts prepared **2a**−**f**.[10]

The stereochemistry of the exo and endo adducts was unequivocally determined through NMR spectral data (^{1}H NMR, ^{13}C NMR, DEPT, HMQC, HMBC)[9] and, additionally, for adducts **2a** and **2b** through 1 D NOE NMR experiments[9] at room temperature. The NOE effects observed between 3-H and the corresponding protons in the close vicinity, shown in Figure 2, allow an unambiguous attribution of the referred structures. The observed exo/endo ratio (~3:1) could be

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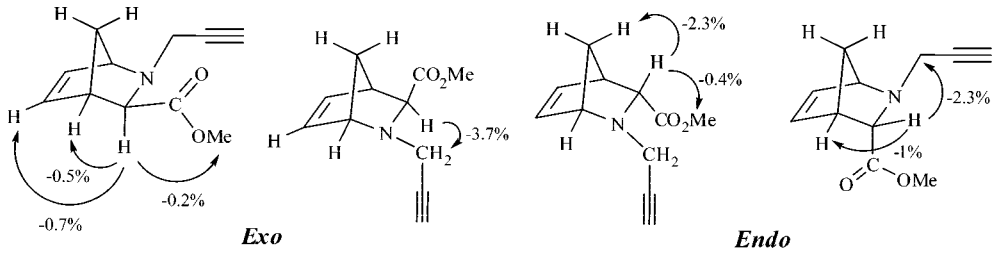


Figure 2. Assignment of the stereochemistry of exo/endo adducts based on 1 D NOE NMR.

Scheme 1. Synthesis of exo and endo (±)-R^1-2-Propargyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates

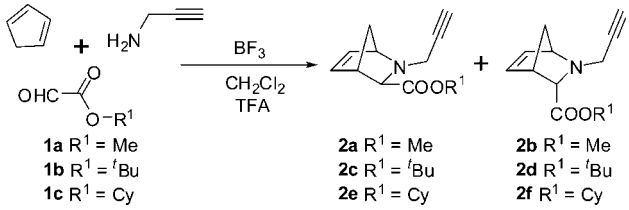


Table 1. Isolated Yields of (±)-2-Propargyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates **2**

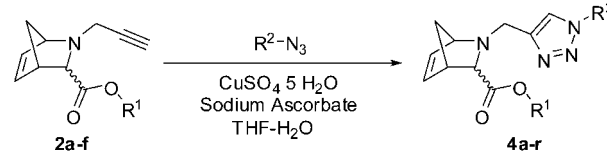
		yield (%)	
compound	R^1	exo	endo
2a	Me	68	
2b			20
2c	^{t}Bu	53	
2d			18
2e	Cy	55	
2f			15

explained considering that in the close vicinity of the C=N bond of the iminium ion (E configuration) the methylene group (Csp^3) exerts a larger steric hindrance than the ester moiety (Csp^2). Consequently, to minimize stereochemical interactions between the methylene group of the diene and the propargyl group, the approach diene−dienophile must occur in an exo manner. That is to say that the stereochemical factors are more important than secondary orbital interactions between the π-systems of cyclopentadiene and the ester group in the dienophile.

Once a set of exo and endo (±)-2-propargyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates **2a**-**g** was available, the structural decoration/modification of the bicyclic scaffold, through construction of the 1,2,3-triazole nucleus, was initiated. For this purpose we made use of the well established copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes,[10] to date the most reliable click reaction.[11] Its applications in numerous areas has highlighted the value of its mild reaction conditions, enabling the practical and efficient preparation of 1,4-disubstituted 1,2,3-triazoles from an unprecedent range of substrates, with excellent selectivity.[10d] The Cu^I-catalyzed Huisgen reaction has emerged as a tailored transformation to either undertake the structural diversification of privileged scaffolds[12] or establish linkages between different molecules.[13]

The first stage of the study involved a comprehensive screening process, in order to identify a mild and efficient procedure able to assemble the 1,2,3-triazole ring, within the plethora of published protocols to perform the Cu^I-catalyzed Huisgen reaction.[10d,12,13] In a pilot experiment, the reaction

Scheme 2. Synthesis of 1,2,3-Triazole-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate Conjugates under the Cu^I-Catalyzed Huisgen Cycloaddition



R^1 = Me, ^{t}Bu, Cy, R^2 = Bn, CH2-COOEt, CH2-S-Ph

Table 2. Isolated Yields of 1,2,3-Triazole-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate Conjugates

			yield (%)	
compound	R^2	R^1	exo	endo
4a	Bn	Me	86	
4b	Bn	Me		79
4c	Bn	^{t}Bu	81	
4d	Bn	^{t}Bu		72
4e	Bn	Cy	83	
4f	Bn	Cy		73
4g	CH_2-COOEt	Me	74	
4h	CH_2-COOEt	Me		63
4i	CH_2-COOEt	^{t}Bu	68	
4j	CH_2-COOEt	^{t}Bu		61
4k	CH_2-COOEt	Cy	76	
4l	CH_2-COOEt	Cy		68
4m	CH_2-S-Ph	Me	78	
4n	CH_2-S-Ph	Me		67
4o	CH_2-S-Ph	^{t}Bu	64	
4p	CH_2-S-Ph	^{t}Bu		54
4q	CH_2-S-Ph	Cy	68	
4r	CH_2-S-Ph	Cy		56

of benzyl azide (**3a**) with the exo (**2a**) and endo (**2b**) adducts of the methyl ester derivative was employed as a model system. Systematic evaluation of the optimum experimental conditions to achieve the proposed transformation included the screening of diverse catalytic copper species (CuCl, CuBr, Cu(0), $Cu(OAc)_2$, $CuSO_4$), solvents (THF, *i*-PrOH-H_2O, DMF, *t*-Bu-H_2O) and other additives (e.g., TEA, DIPEA, or sodium ascorbate). These preliminary experiments evidenced the superiority of the $CuSO_4$/sodium ascorbate system to perform the Huisgen [3 + 2]-cycloaddition on the polyfunctional frameworks **2**. These optimized conditions were successfully applied to the reaction of adducts **2** with the azides (**3a**−**c**) selected for method development. Reactions occurred at room temperature and were usually finished in less than 3 h, generating a library of 18 new 1,2,3-triazole-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate conjugates **4** (Scheme 2, Table 2).[9,14]

As observed (Table 2), independently of the structural differences within the azide precursors (**3**) and the alkoxy residue in the ester moiety of the 2-azabicycle (**2a**−**e**), the yield of the 1,2,3-triazole derivatives obtained from the exo

adducts is slightly superior (~10%) to those prepared starting form the endo adducts. A possible explanation for this finding may be related to the instability of the endo adducts, which suffer a slow degradation under experimental conditions.

In summary, a simple and efficient procedure allowing the rapid assembly of libraries of pharmacologically valuable 1,2,3-triazoles, containing proline mimetic structures, has been developed. Furthermore, the potential of the combination of two highly versatile cycloadditions (e.g., aza-Diels−Alder and the Cu^{I}-catalyzed Huisgen reaction) as a successful strategy to explore new diversity space and address the structural decoration of privileged scaffolds has been established. Further studies to extend these procedures to homopropargylamines as well as other cyclic dienes and glyoxylates, are currently in progress in our laboratories.

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Supporting Information Available. Detailed experimental procedures, spectroscopic data, and copies of NMR and mass spectra for all compounds described. This information is available free of charge via the Internet at http://pubs.acs.org.

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(8) General procedure for the synthesis of *N*-propargyl-2-azabicyclo[2,2,1]hept-5-ene-2-carboxylates **2a**−**f**: A solution of propargyl amine (3.20 mL, 47 mmol) in dry CH_2Cl_2 (30 mL) was added under argon to a stirred suspension of glyoxylate/hydrate (47 mmol) and 3 Å molecular sieves (29 g) in dry CH_2Cl_2 (140 mL) at 0°C. When the addition was complete the reaction mixture was cooled to−78°C and treated successively with trifluoroacetic acid (3.60 mL, 47 mmol), boron trifluoride etherate (5.90 mL, 47 mmol), and freshly distilled cyclopentadiene (7.5 mL, 91 mmol). After 6 h, saturated aqueous $NaHCO_3$ solution (120 mL) and then solid $NaHCO_3$ (12 g) were added. The reaction mixture was allowed to reach room temperature and filtered through a pad of Celite, and the organic layer of the resulting mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The pooled organic layers were washed with saturated aq $NaHCO_3$ solution (3 × 100 mL) and brine (3 × 100 mL) and were dried over Na_2SO_4. Removal of the solvent on a rotary evaporator left an oily residue that upon chromatography on silica gel using a (19:1) hexane/EtOAc mixture as eluent afforded pure exo-adduct in the early fractions and the endo-adduct in the latter ones, both as colourless oils.

(9) Complete description of the spectroscopic and analytical data of all compounds described is included in the Supporting Information.

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(14) General procedure for the Cu-catalyzed Huisgen cycloaddition between *N*-propargyl-2-azabicyclo[2,2,1]-5-ene-2-carboxylates (**2a**−**f**) and azides (**3a**−**c**): To a Kimble vial containing a solution of the *N*-propargyl-2-azabicyclo[2,2,1]hept-5-ene-2-carboxylates **2a**−**e** (0.38 mmol) in 3 mL of a THF/H_2O (5:1), a mixture of the corresponding azide (**3a**−**c**) (0.38 mmol), sodium ascorbate (0.08 mmol), and $CuSO_4 \cdot 5H_2O$ (0.04 mmol) were added. The reaction mixture was orbitally stirred, at 40°C, until reactions reached completion (2−5 h), filtered through a Celite pad, and successively washed (5 mL) with THF, CH_2Cl_2, MeOH, and AcOEt. Evaporation of the solvents afforded an oily residue that was diluted with CH_2Cl_2 (10 mL), treated with PS-TMG (500 mg), and stirred for 0.5 h to remove the copper salts. Isolation of the desired 1,2,3-triazoles **4a**−**r** was accomplished by preparative chromatography.

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