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Biological activates of 1,2,3-Triazole in Heterocyclic Compounds

Smit B Patel and V.G. Patel
Department of Chemistry, Municipal Arts and Urban bank Science College, Mehsana, Hemchandaracharya North Gujarat University, Patan, Gujarat, India

ABSTRACT
1,3-Dipolar cycloaddition reactions can be considered a powerful synthetic tool in the building of heterocyclic rings, with applications in different fields. In this review we focus on the synthesis of biologically active compounds possessing the 1,2,3-triazole core through 1,3-dipolar cycloaddition reactions. The 1,2,3-triazole skeleton can be present as a single disubstituted ring, as a linker between two molecules, or embedded in a polyheterocycle. The cycloaddition reactions are usually catalysed by copper or ruthenium. Domino reactions can be achieved through dipolarophile anion formation, generally followed by cyclisation. The variety of attainable heterocyclic structures gives an illustration of the importance of the 1,2,3-triazole core in medicinal chemistry.

Keywords : Nitrogen Heterocycles, Enzyme Catalysis, Biological Activity, Medicinal, Chemistry

I. INTRODUCTION

The identification of these rapid synthetic strategies should allow the medicinal chemist to assemble a large number of potentially active compounds.

1,2,3-triazole ring, also known as Huisgen cycloaddition. Although this reaction was discovered at the beginning of the 20th century, its real potential and mechanism of reaction were uncovered only in the 1960s, by Huisgen et al.[1] Huisgen's work led to the postulation of a synthetic route that could provide a huge variety of chemical structures in a very short time with different and, at the same time, outstanding biological properties, giving enormous energy to modern drug discovery.

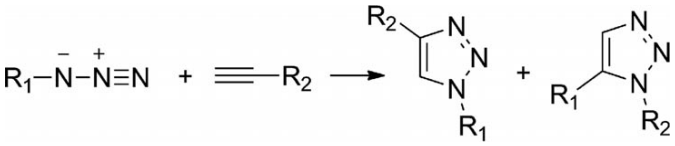
THE 1,2,3-TRIAZOLE RING IN MEDICINAL CHEMISTRY

SYNTHESIS OF 1,2,3-TRIAZOLES THROUGH 1,3-DCRS

The 1,2,3-triazole core, often found in heterocyclic structures with biological activities, plays different roles: as a disubstituted bioisostere (generally in the 1,4-positions), as a linker of two biologically active molecules, or as a core embedded in a polycyclic skeleton. The synthesis of the triazole core, through 1,3-DCRs, can be performed by catalytic or non-catalytic synthetic pathways. Interestingly, structural and energetic details of the reaction mechanism of a 1,3-DCR can be obtained by DFT calculations, as recently reported.[2] Such an approach could be promisingly extended to the study of metal-catalyzed 1,3-DCRs.

1, 4-DISUBSTITUTED 1,2,3-TRIAZOLES

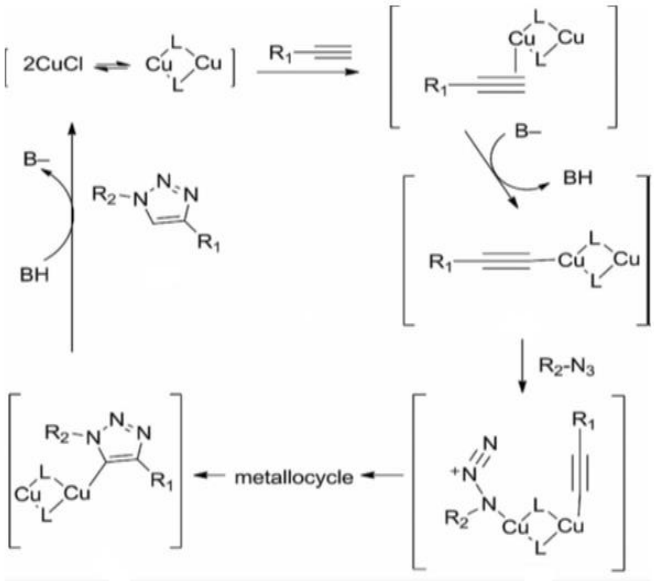
Cycloaddition of azides**(A)** and terminal alkynes **(B)**, to build 1,2,3-triazoles **(C)** and **(D)**, represents an important class of 1,3-DCRs with wide applicability in the synthesis of heterocyclic biologically active compounds.



(A) (B) (C) (D)

The potential of this reaction type is very high, because alkyne and azide moieties can be incorporated into a wide range of compounds. However, for more than 40 years this reaction suffered from a lack of selectivity, yielding mixtures of the 1,4- and the 1,5-regioisomers.[3] Furthermore, this transformation requires heating and long reaction times to reach completion and the two regioisomers are sometimes laborious to purify by classical chromatographic procedures.

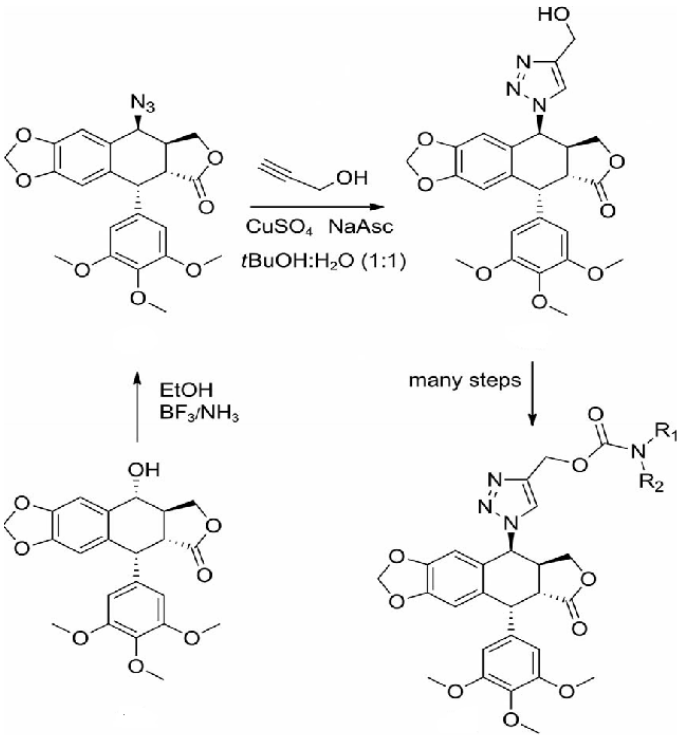
This aspect is interesting because, as shown below, the catalytic properties of copper metal or salts can be attributed to the reversible CuII–CuI reaction and to the coordination chemistry properties of CuI,II complexes with the reaction intermediates of 1,3-DCRs.



Proposed reaction mechanism of Cu[1]-catalysed 1, 3-DCRs.

In this case the chemical modification involved the incorporation of the 1, 2,3-triazole moiety at the C-3 position of ring A, with the aim of studying the antiproliferative activity of triazolyl-steroids. With this unusual solvent system a library of 18 triazole derivatives, offering structural diversity, was prepared in very high yields.[4] These compounds were screened against a panel of nine human cancer cell lines, and many produced dose-dependent growth inhibition effects on several cancer cell lines.[4]

The same unusual solvent mix (*t*BuOH/H2O 1:1) was also crucial in another interesting synthesis route to obtain, through CuAAC reactions, a series of carbamate derivatives of 4β-(1,2,3-triazol-1yl) podophyllotoxin.[5] Podophyllotoxinis a strong antimicrotubule agent as an inhibitor of the colchicine-binding site on tubulin; however, because of its high toxicity, it could not be used in therapy.[6] All of the synthesised carbamates showed more potent anticancer activity, higher solubility and less toxicity than natural podophyllotoxin against a panel of four human cancer cell lines.[5]



Synthesis of carbamate derivatives

THE TRIAZOLE RING AS SPACER OR LINKER

The triazole moiety is an ideal linker: it provides great water solubility and is very similar to amide bonds (see above) and relatively resistant to hydrolysis reactions,[7] so it is stable enough under typical biological conditions. Moreover, this ring is extremely rigid, and for this reason the two linked substances cannot interact between themselves.[7] These features allow the triazole moiety to be seen as an inactive linker or spacer, although it is not possible to exclude the possibility that, under particular conditions, it may act as a biological entity on its own.

II. CONCLUSION

This review has surveyed the occurrence of the 1,2,3-triazole nucleus in biologically active heterocyclic compounds. The synthesis of such compounds is achievable through 1,3- dipolar cycloadditions through both catalytic and uncatalytic routes. In the former case, copper-catalysedazide–alkyne cycloaddition (CuAAC) is the most efficacious: a click reaction characterized by high reliability and total specificity in producing the 1,4-disubstituted triazoleregio isomers. Other innovative synthetic approaches to 1,2,3-triazoles, such as engineering enzymatic strategy.

The biological importance of the 1,2,3-triazole system as a linker between two active molecules to improve their pharmacokinetic and or pharmacodynamic profiles has also been discussed.

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