Journal of Analysis and Computation (JAC)
(An International Peer Reviewed Journal), www.ijaconline.com, ISSN 0973-2861
Volume XVII, Issue II, July-Dec 2023

SPIRO-HETEROCYCLES: SYNTHESIS & COMPUTATIONAL STUDY

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ABSTRACT

Heterocycles have achieved a prominent place among various classes of organic compounds for their diverse biological and medicinal activity.
In the present paper a facile synthesis of spiroazabicycloadducts has been accomplished by [3+2] cycloaddition reaction of azomethine ylides, generated from 3-methyl-cyclopentane-1,2-dione and different secondary cyclic amino acids, with electron-deficient dipolarophiles in 62-70% yield. DFT calculations have been performed to understand the stereochemical course of the cycloaddition reactions. The products have been characterized by physical and spectroscopic techniques.

Keywords: 1,3-dipolar cycloaddition, azomethine ylides, dipolarophile, spiroheterocycles, stereoselectivity, spectral characterization, DFT calculations**.**

[1] INTRODUCTION

Heterocyclic compounds are of very much interest in our daily life1. Heterocyclic compounds have one or more hetero atoms in their structure. Wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. These are common fragments of the vast majority of marketed drugs. This is a reflection of the central role that heterocycles play in modern drug design. They can serve as useful tools to manipulate lipophilicity, polarity, and hydrogen bonding capacity of molecules, which may lead to improved pharmacological, pharmacokinetic, toxicological, and physicochemical properties of drug candidates and ultimately drugs2-3.
New advances in synthetic methodologies that allow rapid access to a wide variety of functionalized heterocyclic compounds are of critical importance to the medicinal chemist as it provides the ability to expand the available drug-like chemical space and drive more efficient delivery of drug discovery programs. Heterocycles are a good choice when designing

molecules that will interact with targets and disrupt the biological pathways associated with cancer progression.
Various α-dionehave exhibited various pharmacological activities like antioxidant, antitumoiur, antimalarial and antiviral.17For example synthetically phenanthrenequinone has been reported to undergo several types of reactions.18- 20 Thus in pursuit of this theme we have examined the 1,3-dipolar cycloaddition reactions with amino acids viz thiazolidine-2-carboxylic acid (TCA) and the results are presented here4-6.

[2] RELATED WORK

Due to their prevalence in nature as well as their structural and chemical diversity, heterocycles playan immensely important role in anti-cancer drug discovery. Their inclusion in approximately two- thirds of the anticancer drugs approved by the FDA in the first half of this decade highlights their ongoing importance in cancer research, with research demonstrating time and again the central role they have to play in the fight against cancer.

The use of compound screening collections with a strong focus on heterocyclic-based structures cannot only lead to the identification of a wide numberof potentially successful drug candidates, but can also fast-track the drug development process, ultimately saving time, money and resources.

Biological activities

Antifungal activity Fungi are heterotrophic microorganisms that are distinguished from algae by lack of photosynthetic ability. Fungi includes both yeast and moulds. The former are spherical, oval and mucosid colonies in agar medium and the latter consists of elongated cells that usually reproduce by budding and forming branches of cells.

a) F.Russo et al have synthesized thiadiazolo pyrimidines (i) and their hydrazines (ii) R=$CF_3C_6H_4$,2-$OEtC_6H_4$ and 4-$NO_2C_6H_4$.

b). Ahluwalia et al have synthesized 5-(3',4'-dihydro-2',2',8'-trimethyl-2'H-1'-benzopyran-7-yloxymethyl)-4-phenyl-1,3,4-triazole-3(4H)- thiol (III)which shows significant antifungal activity. R=C_6H_5, mcl-C_6H_4, pcl-C_6H_4, m-or pCH_3- C_6H_4, pCH_3O- C_6H_4.R_1=CH_3, C_6H_5, R2=H, CH3.

Anti-inflammatory: Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system. Non-steroidal anti-inflammatory drugs (NSAIDs), some common examples of NSAIDs are: aspirin, ibuprofen, and naproxen.
Antibacterial: Bacteria are the simplest and smallest unicellular organisms found individually or in clusters. The multitude of highly effective and relatively non-toxic drugs available for the treatment of bacterialinfections have provided tough competition for the medicinal chemist, attempting synthesis of new antibacterialagents.

a). Sen Gupta et al have synthesized (xviii),some thiazine derivatives and found antibacterial agents.

Ant allergic: A number of heterocyclic compounds have shown the ant allergic activity.

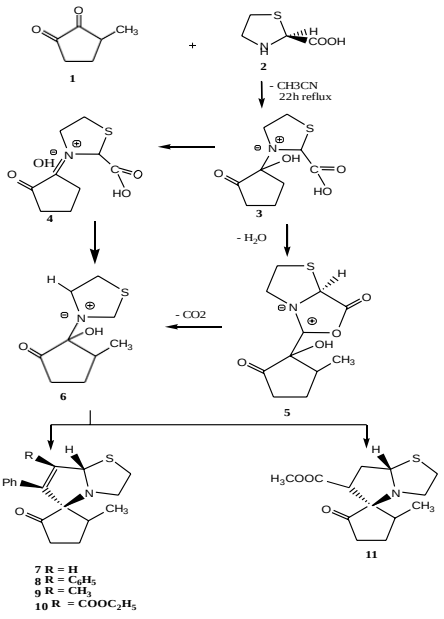
a). Musser et al have synthesized 2-(2, 3-dihydro-2-oxo-1, 3 ,4-oxadiazol-5-yl) benzoheterocycles (xxix), (xxx). In compound xxix X=O, NMe, CCl, CH, CMe; X'=N, S, CH_2, NH; R=H, Ac, CO_2Et, Me etc. R'=H, 5-Cl', 5-(CO_2Me), 5-CO_2Et and in compound xxx R^2=H, CO_2ET

[3] EXPERIMENTAL

A mixture of 3-methyl-cyclopentane-1,2-dione **(1)** (0.34g, 3.0 mmol), and thiazolidine-2-carboxylic acid (TCA) **(2)** (0.4g, 3.0 mmol), in equimolar ratio in dry acetonitrile (50 ml) was heated to reflux under nitrogen atmosphere for 22h in a 100 ml round bottom flask. It was judged complete by TLC, unreacted acid was filtered off from the cooled reaction mixture and the filtrate was evaporated in *vaccuo*. The concentrated reaction mixture was allowed to stand overnight. However, no crystallization occurred and therefore the crude product was subjected to column chromatography over silica gel by elution with solvents of rising polarity. The compound **(5)** was obtained from chloroform/ethylacetate fraction (2:1) as dark brown solid yield 64%,

[4] RESULT & DISCUSSION

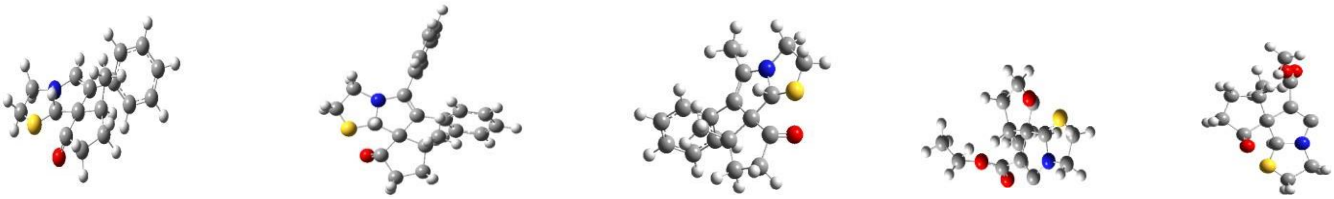
The reaction of 3-methyl-cyclopentane-1,2-dione **(1)** with thiazolidinone-2-carboxylic acid **(2)** was carried out in the molar ratio of 1:1 in dry acetonitrile whereby it afforded (2S, 5S)-spiro-{1-aza-3-oxa-7-thia-bicyclo-[3,3,0]-octane-5'-methyl-2,1'-pentane}-2'-onein 70% yield. The reaction occurs probably *via* the formation of intermediate ketohydroxy acid **(3)** as depicted in **(Scheme 1.1).**



Scheme 1

The structures of all the spiroazabicycloadducts have been ascertained from their spectral data. The stereochemistry of all other cycloadducts **(8-11)** was decided analogously by detailed DFT calculations. From these studies it emerged that following regioisomers **(8-11)** should be formed predominantly.

The optimized geometries of all cycloadducts **(8-11)** are shown in **(Fig. 2.3)**.



(7) **(8)** **(9)** **(10)** **(11)**

Figure 1: Optimized geometries of cycloadducts (7-11)

[4] SUMMARY

In this paper we have synthesised spiroheterocycles derived from 3-methyl-cyclopentane-1,2-dione with thiazolidinone-2-carboxylic acid in presence of various dipolarofiles using 1, 3 Dipolar cycloaddition reaction. The structures of all the spiroazabicycloadducts have been ascertained from their spectral data viz. Ir, NMR etc. The stereochemistry of all other cycloadducts was decided analogously by detailed DFT calculations. From these studies it emerged that following regioisomers should be formed predominantly.

The rate at which heterocyclic compounds continue to be invented testifies to the strength and vitality of this area of organic chemistry. The challenges of discovering new heterocyclic systems and of understanding their properties also continue to stimulate research in the area.

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