Original Article

Synthesis Of Novel System Spiro-Heterocyclic By Diels-Alder Reaction Catalysed With $TiCl_4$ For [4+2] Cycloaddion

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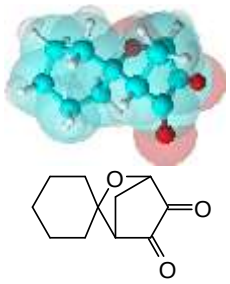
Abstract

We have developed a novel system of organic spiro-heterocyclic compounds: like **diazaspiro- [5.5] undec-8-ene** and **oxaspiro [bicyclo [2,2,1] heptane-2,1-cyclohexane] dione** system with the reaction of Diels-Alder catalyzed with $TiCl_4$ in high regio and stereo-selective way and excellent yield. Initially, we developed different dienophiles and confirmed their structures by spectroscopic methods, ^{1}H NMR, ^{13}C-NMR.then we studied the mechanistic and stereo-chemical action of the various dienophiles concerning the dienes. Finally, the structure of the various newly synthesized products was established by the spectroscopic methods: ^{1}H-NMR, ^{13}C-NMR, the stereochemical aspects of the Diels-Alder reaction, and cycloaddition [4 + 2] were established, and the reaction conditions were mentioned.[16, 17]

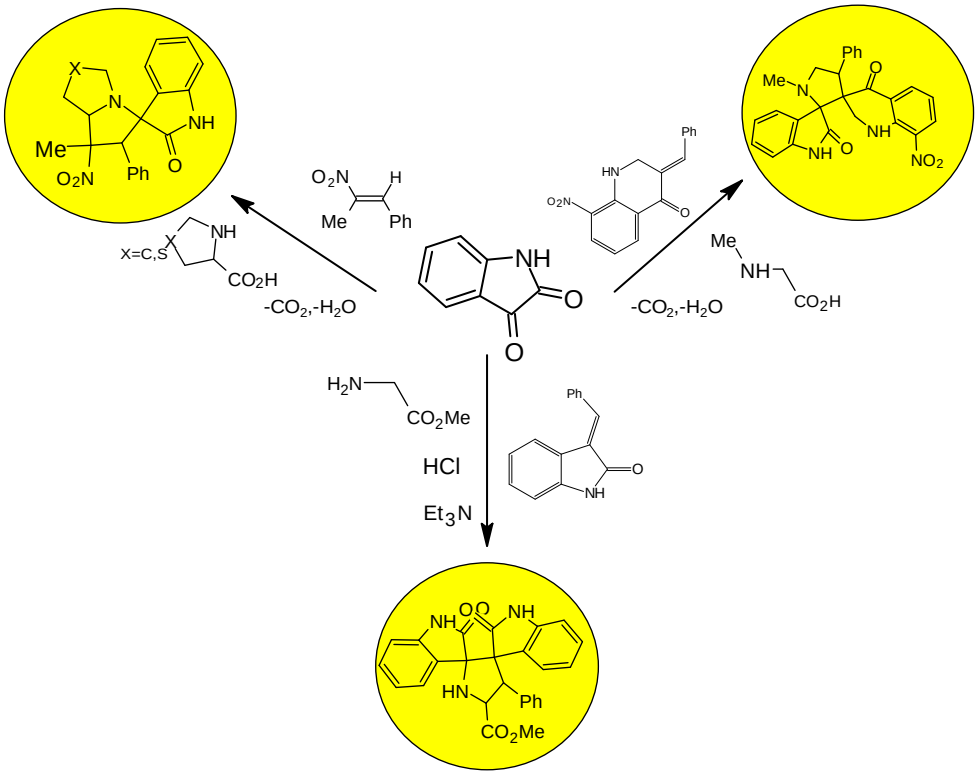
Diazaspiro-[5.5]undec-8-ene



Oxaspiro[bicyclo[2, 2, 1]-heptane-2, 1-cyclohexane]dione

The spiro[pyrrolidine-2,3,0-oxindole] core is a privileged heterocyclic ring system, which is featured in a large number of bioactive naturally occurring alkaloids and also in some compounds synthesized for medicinal purposes. Among the various N-hetero-cycles, spirooxindol derivatives are widespread in numerous natural products and are pharmacologically important compounds.[2,3]

Spiro-molecules are molecules made up of a variety of azomethine yieldes and alkenes in high regio- and stereo-selective **Scheme 1**, and contain a range of important bioactivities such as antitumor activities, antiinflammatory, antibacterial, antimicrobial, antituberculosis, and acetylcholinesterase inhibitors.[6,7] Recently, the multicomponent cycloaddition 1, 3-dipolar 2, 3, 0-oxindoles have been used as a strategy for the synthesis of different types of spiro (**Figure1)**.[1]



Scheme 1. Multicomponent 1, 3-dipolar cycloaddition for the synthesis of spiro-[pyrrolidine-2, 3, 0 -oxindole] derivatives.

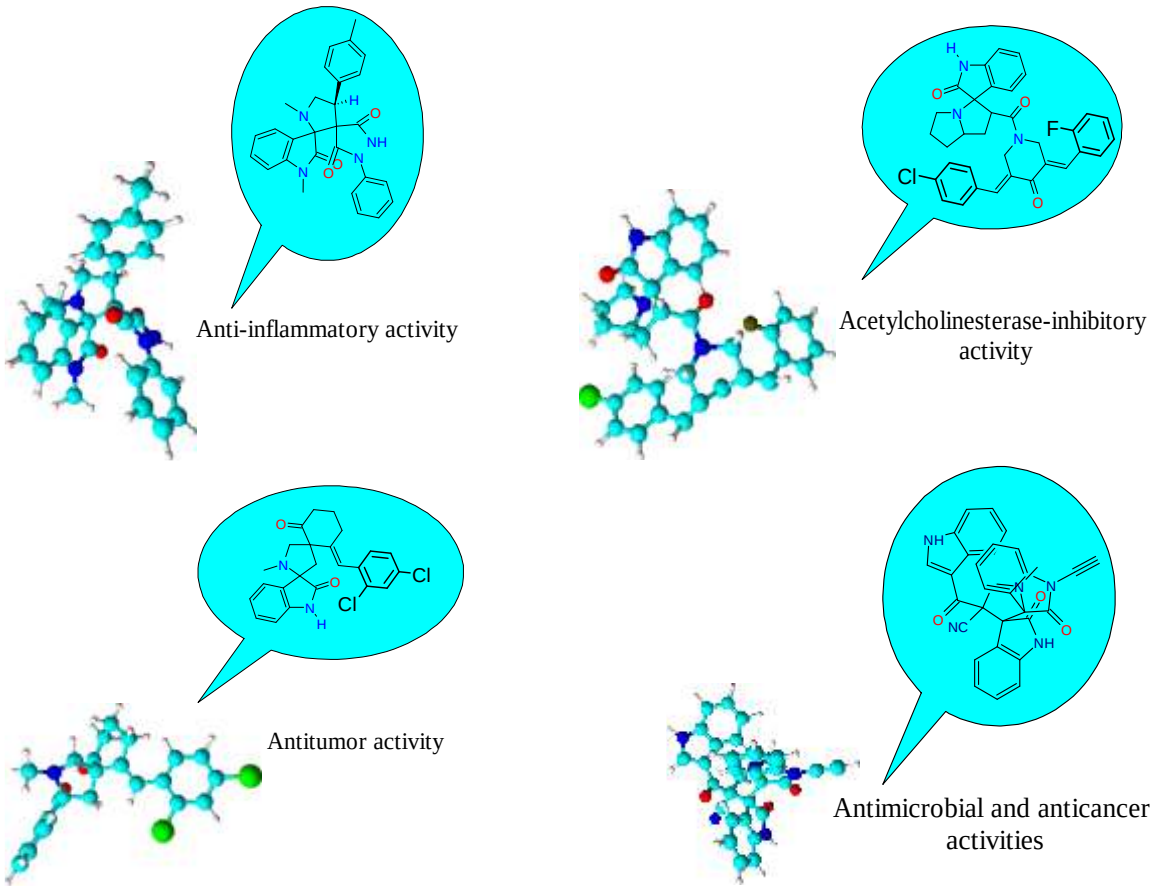
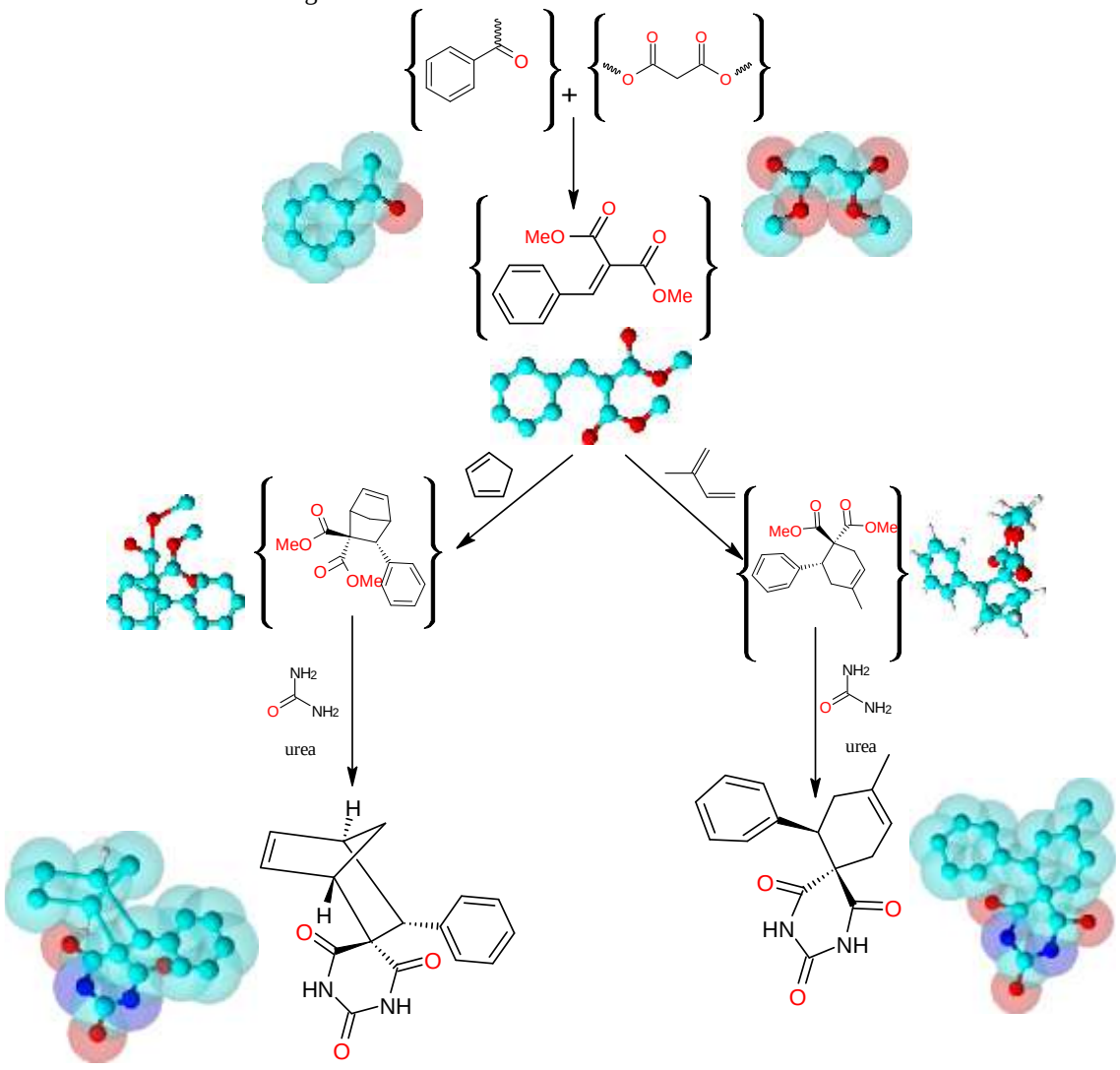


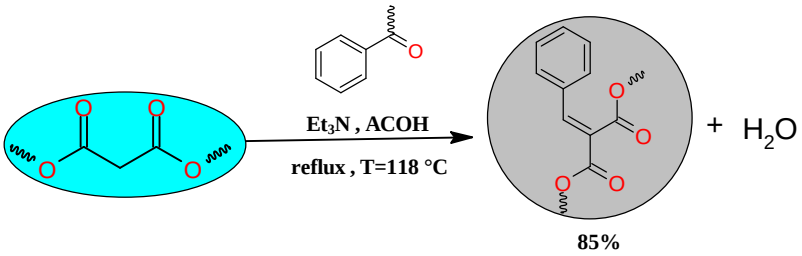
Figure1. Some examples of biologically active compounds containing the spiro-[pyrrolidine-2, 3,0 -oxindole] motif

Spiro-heterocyclic compounds are widely applied in the pharmaceutical and chemical industries as building blocks or grouped into molecular libraries.[4,5,6] This work provides a new family of such compounds in which one of the cycles is a cyclobutane group with an alkenyl substituent group (C=C) in the second position.[18,19,20] These compounds can be used as scaffolding to contain other structures of high pharmaceutical importance.[21, 22, 23] In addition, this alkenyl substitution group increases the rigidity of the structure, which is one of the most important attributes in the synthesis of new drugs.[24] Spiro-heterocyclics represent stimulating targets in both natural product chemistry and theoretical chemistry,and the construction of quaternary carbon centres remains a fundamental test of the synthesis methodology.[9] The undecane spiro[5,5] system has particularly attracted the attention of many synthetic chemists.[25,26] This work provides an effective and practical new method for constructing the skeleton of the undecane spiro[5,5], the undec-8-ene diazaspiro-[5,5], and the dione oxaspiro[bicyclo[2,2,1] heptane-2,1-cyclohexan] system, the Spiro[bicyclo [2,2,1] system, 2,5-heptane-pyrimidine] trione, with two known reactions, under single conditions.[27]This research project aims to create new oxygenated and multifunctional nitrogen spiro-cycles in a diastereo and enantioselective manner, obtained in particular by the reaction of Diels- Alder catalyzed by $TiCl_4$ via a cycloaddition [4+2].[28] From what we have mentioned before, here we show the importance of spiro-cyclic compounds to reach chiral centres, and the role that the Lewis acids may have played as a catalyst in the Diels -Alder reaction; improves the stereochemistry increase the yields of the products to be produced. The choice of our strategy is based on the use of two known reactions: the first reaction is aldolisation (Knoevenagel condensation) and the second is the Diels-Alder reaction these tow reactions done under simple and efficient conditions according to:



Scheme 2. General synthesis of new spiro-heterocyclic compounds

In our case, the condensation of Knoevenagel between the aromatic aldehydes and the 1,3 dicarbonyl compound allowed as to obtain the starting product. From the latter with the different diene such as isoprene .etc, we tried to synthesize other products by the Diels-Alder reaction catalysed by $TiCl_4$.[29,30] We have chosen the aromatic aldehydes as electrophilic source and the 1,3 dicarbonyl as nucleophilic source in presence of the base triethyle amine to remove the proton and dissolved in acetic acid at reflux the reaction mixture obtained is reacted by the method described in the experimental part to extract the target compounds according to:



Scheme 3 . The compound resulting from the condensation of Knoevenagel

DETERMINATION OF PRODUCTS STRUCTURES

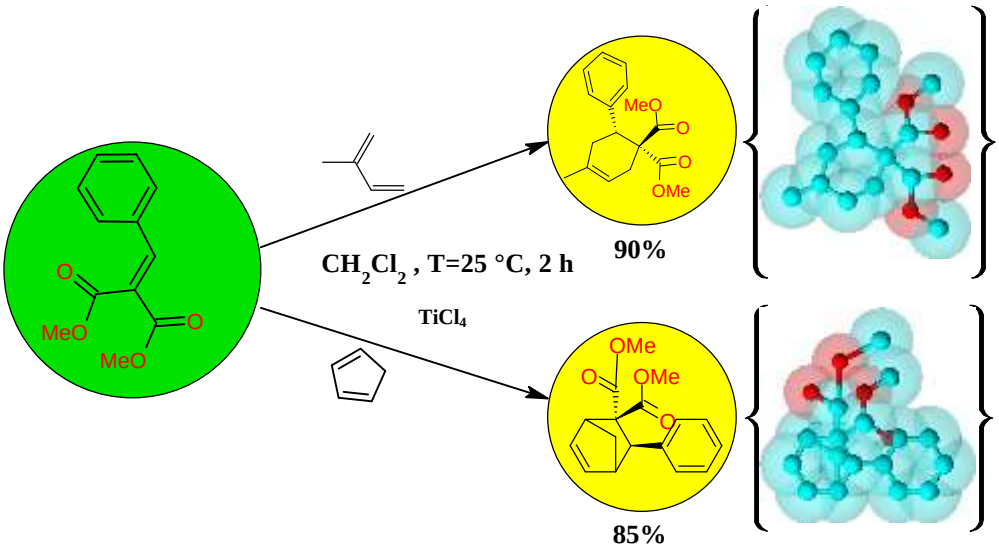
These result allow us to make the following remarks: All the tests of condensation of the 1,3 dicarbonyl compounds gave interesting yields, -not optimized-, (between 85% and 90%) taking into account the use of not very expensive commercial reagents. The IR, ^1H NMR, ^{13}C NMR spectroscopic analysis gave us satisfactory results. Example: The disappearance of a peak at 10 ppm corresponds to the proton of the aldehyde function. Shows that the latter has reacted.[32]

- The appearance of a singulet peak at 8, 5 ppm corresponds to the vinyl proton.
- The appearance of the carbon Sp^2 shows the formation of double bond.

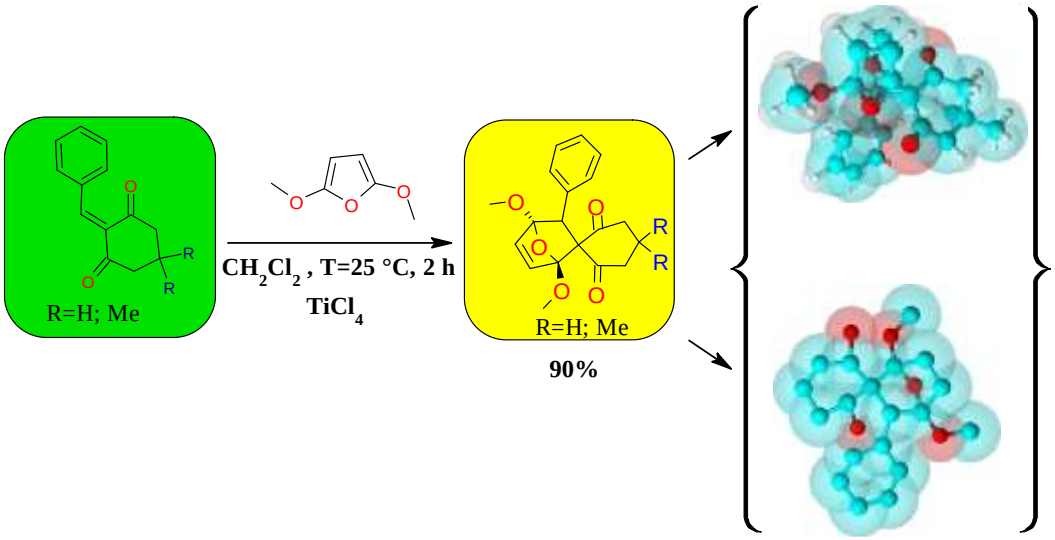
The condensation between the aromatics aldehydes and the 1,3 dicarbonyle compounds led to the expected condensed products with high yield the synthesized product was all identified by the spectroscopic methods NMR ^1H, NMR ^{13}C, Dept.

SYNTHESIS OF SPIRO-HETEROCYCLIC COMPOUNDS BY DIELS ALDER REACTION

Our goal was the preparation of spiran compounds by the **Diels-Alder** reaction catalysed with **$TiCl_4$** (because it avoids overheating the reactants, and protects the two carbonyls), with the products condensed by aldolisation as a **dienophile** according to the following reactions:



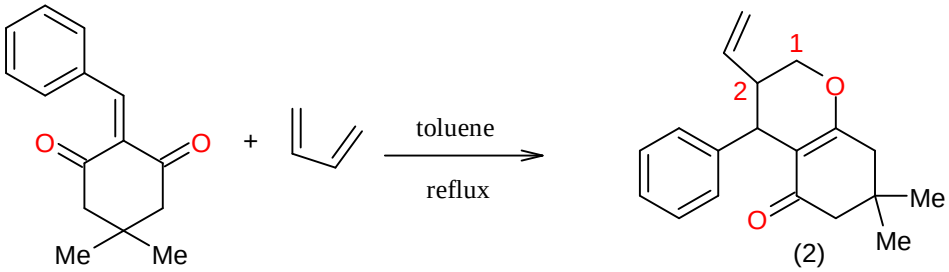
The Synthesis of cyclic compounds by Diels-Alder Reaction



Scheme 4 . The synthesis of spiro-heterocyclic compounds by Diels-Alder reaction

Thin layer chromatography confirmed the formation of a new product by this reaction. The presence of the proton H (5.83 ppm, t,vinyle, J=10.04 Hz,1H), H(1.97 ppm , s, CH_3,3H), H (4.00 ppm , t, ^{3} J=8.55 Hz, 1H), in the NMR spectra and of the C spiro (77.49 ppm) carbon in the ^{13}C NMR spectrum shows that the compound formed is the target product.

The $TiCl_4$ in this reaction plays a very important role not only it accelerates the reaction but also protects the carbonyl groups otherwise we will have another type of reaction, that of the hetero Diels-Alder reaction and the synthesized compounds will not be spiran compounds.[30]



Scheme 5. The synthesis of the polycyclic compounds by the hetero Diels-Alder reaction

- But in the spectra of C^{13} NMR we do not observe the signals which correspond to carbon **1** and **2** which normally resonate between 60 and 111 ppm. The spectroscopic results show that this adduct **(2)** is not formed in our reaction.[35]

- The Lewis acids by their coordination on the free electron pairs of the heteroatom's or the unsaturation reacted, act as a catalyst by lowering the electron density and the BV level of the dienophile and therefore lowering the energy level of the transition state **Figure.2**.[8] The use of catalysts is interesting because it avoids having to heat the reactants too much, which can be fragile. For reactions involving non-symmetrical reagents, the modification of the coefficients in the molecular orbitals driven by the coordination makes it possible to increase the regioselectivity even more. [31]

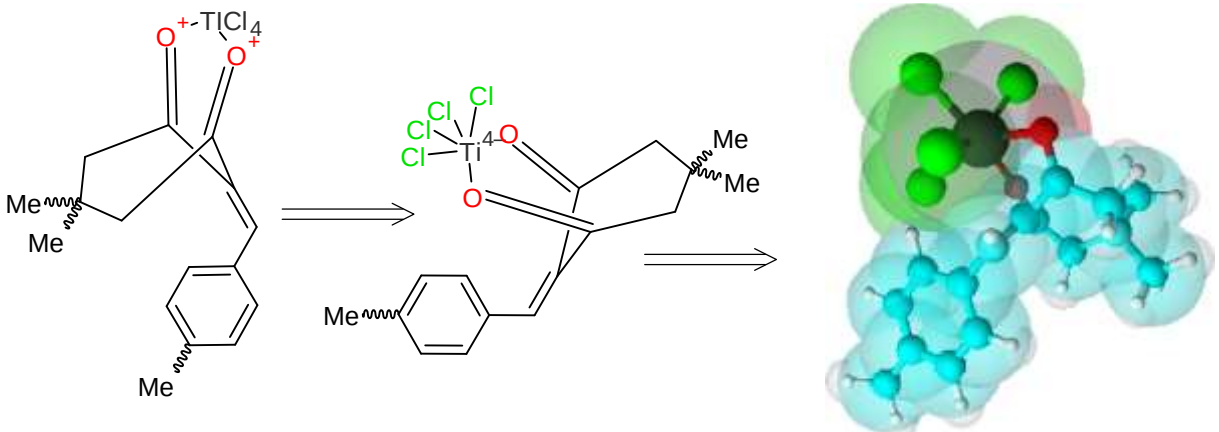


Figure.2: Coordination in 3 D in-plane

- Some crystal structures of chelate complexes have been reported. An O-Acryloyllactate-$TiC1_4$ complex (**Figure. 2**. [9, 10]) has rare out-of-plane (**Figure. 3).**

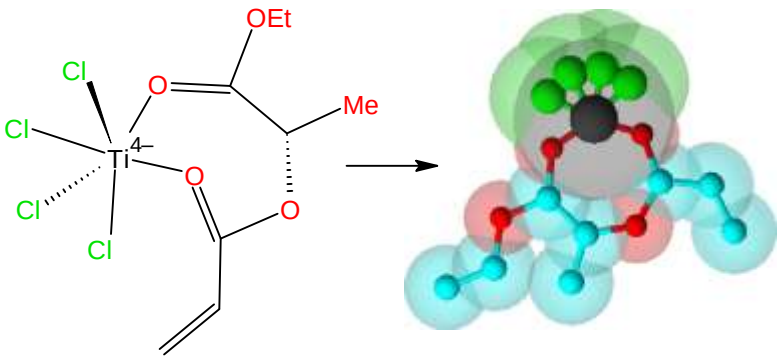
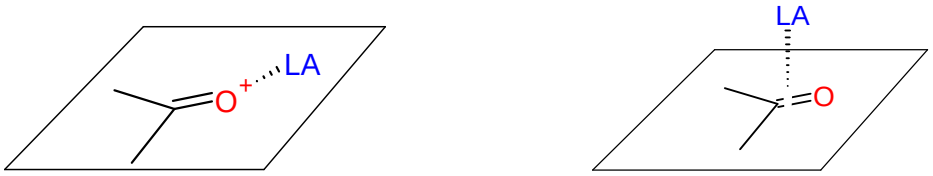


Figure 3. O-Acryloyllactate-$TiC1_4$



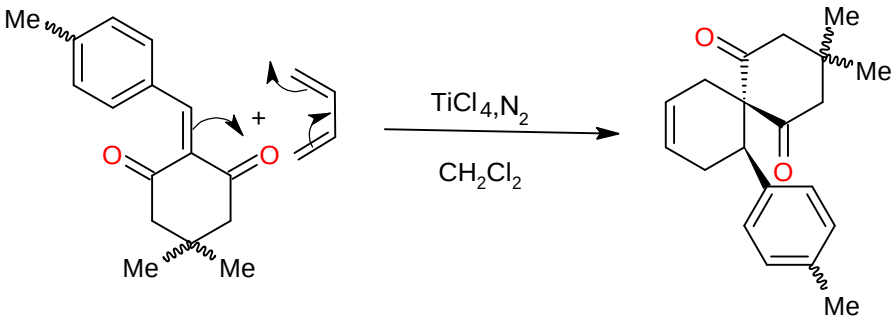
In-plane (σ-bonding) Out-of-plane (¶-bonding)

Figure 4. Mode of coordination

Another advantage of the catalysed version of the Diels-Alder reaction is to be able to make it asymmetric by decorating the catalyst with chiral ligands.[11]

The selectivity increases by organizing the transition state, but also by lowering the temperature. The metals used are most often boron, aluminium, titanium. The asymmetric Diels-Alder reaction is an important synthesis tool, adding the asymmetric character to the other assets of the reaction.[12]

THE GENERAL MECHANISM OF THE DIELS- ALDER REACTION

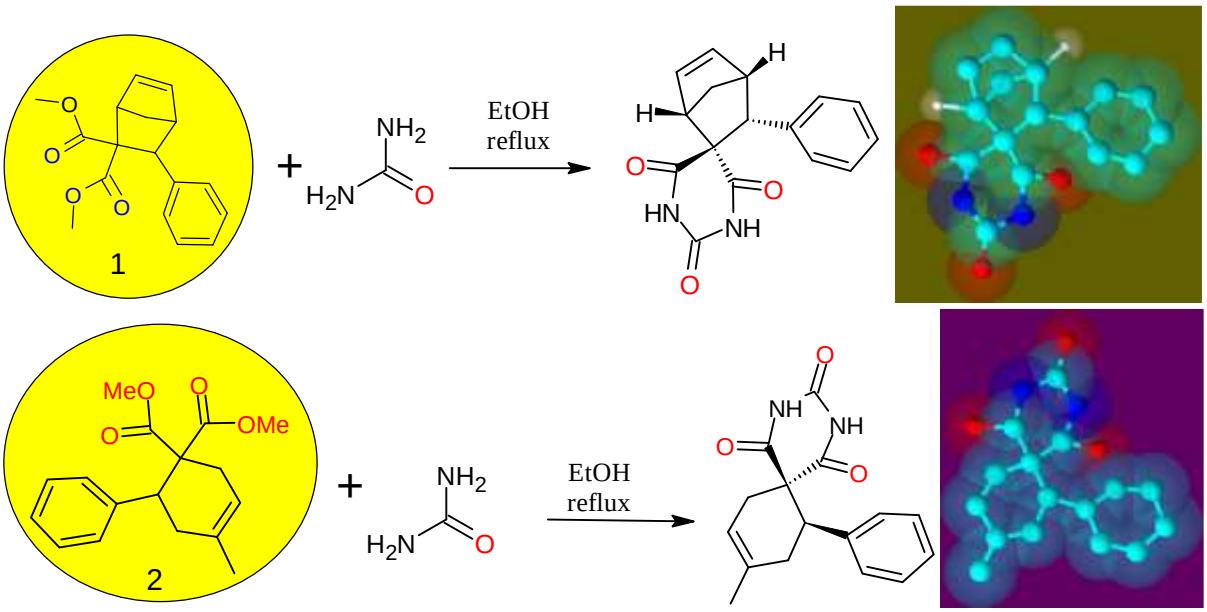


Scheme 6 . The general mechanism of the Diels-Alder reaction

- The mechanism of Diels-Alder is stay the same mechanism only that in the uncatalysed reaction un intermediate does not appear, so that this reaction is rigorously a one-step process.[33, 34]

But in the catalysed reaction the intermediate is more stable so if we can say that the catalyser is responsible for his existence this suggestion made by **Inukai and Kojima**.[18] Noticeable are the very mild conditions of this Diels-Alder addition catalysed with $TiCl_4$: the reagents are dissolved in dichloromethane, stirred at low temperature under inert atmosphere,and the reaction reaches completion after relatively short periods of times (2 h).The use of catalyst is interesting especially for the reactions involving non-symmetrical reactants, the modification of the coefficient in the molecular orbitals caused by the coordination

makes it possible to further increase the regioselectivity such as for example: we used isoprene as an unsymmetrical diene the stereochemistry of this Diels-Alder reaction is also interesting because it produces a substitution (**para**). In the presence of Lewis acid ($TiCl_4$), the reaction can take place at low temperature and the regioselectivity increases to 93:7.[14, 15]
The cyclisation of the two complexes **1** and **2** becomes from the Diels-Alder reaction of the acyclic dienophile with urea and all are dissolved in ethanol at reflux, according to the following reactions:



Scheme 7. Cyclisation of the two complexes 1 and 2 becomes from the Diels-Alder reaction

In summary, the construction of new Spiro-compound with Diels-Alder reaction catalysed with $TiCl_4$ has been successfully developed.

CONCLUSIONS

In conclusion, spiro-Heterocyclic compounds have been developed in view of their importance due to their high biological activities presence in naturally occurring substances, with two different systems; spirodione: **spiro [5,5] undecene skeleton, oxaspirobicyclo [2,2,1] heptane skeleton,** spiro-trione**: diazaspiro [5,5] undecene skeleton, spirobicyclo [2,2,1] heptane-pyrimidin skeleton,** with high regiospecific and stereospecific Diels-Alder reaction catalysed with $TiCl_4$ in excellent yield.
For un upcoming research that opens a new window to study their biological activities.

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