DEGREE OF BILINGUAL CHEMISTRY

# DOMINO REACTIONS IN THE SEARCH FOR A GREENER FUTURE

## BACHELOR THESIS IN CHEMISTRY

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# List of abbreviations

- AcOEt: ethyl acetate
- Approx. approximately
- DABCO: 1,4-diazabicyclo[2.2.2]octane
- DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
- DCM: dichloromethane
- DEPT: distortionless enhancement by polarization transfer
- DMF: *N,N*-dimethylformamide
- DMSO: dimethyl sulfoxide
- d.r.: diastereomeric ratio
- *ee*: enantiomeric excess
- equiv: equivalents
- IR: infrared
- Mp: melting point
- NMR: nuclear magnetic resonance
- rt: room temperature
- $R_f$: retention factor
- TBAF: tetra-*n*-butylammonium fluoride
- TLC: thin-layer chromatography
- UV: ultraviolet

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# 1 Introduction

As times evolve, so does society's environmental awareness. This consciousness has also reached the field of chemistry, exposing the enormous amount of hazardous chemical wastes generated by industries and laboratories and their detrimental environmental impact. This trend leaded to the coining of the term Green Chemistry after the publication of "Green Chemistry, Theory and Practice" by Anastas and Warner, which collected the 12 principles of Green Chemistry. [1] These fundamentals point the way forward to reduce the environmental and health impact of chemical synthesis.

Therefore, current synthetic chemistry demands greener techniques with higher efficiency, yield and selectivity, least intermediate isolation and minimal energy cost and waste generation. [2] In this regard, solvents are responsible for much of the chemical wastes. [3] Thus, using solvent-free synthetic routes or green solvents is an appropriate approach to decrease the environmental impact. [4] Green solvents are those that accomplish as many of the 12 criteria proposed by Gu and Jérôme [5] (such as low toxicity, high recyclability and biodegradability or low flammability) but not necessarily all. [4] Some examples of green solvents are water, ionic liquids or bio-based solvents as glycerol.

Another alternative towards greener synthetic strategies is to improve the atom economy of the procedure. This can be achieved by one-pot methods, as they allow performing several reactions in the same flask without needing to isolate any intermediate. Domino reactions (also called tandem or cascade reactions) are defined as one-pot single-operational procedures, involving at least two bond formation reactions, in which each sequential transformation gives an intermediate with suitable functional groups to go on reacting until reaching the final product. [2,6] Hence, all reagents and catalysts are introduced at the beginning, keeping the reaction conditions constant during the whole process, so only final separation and purification is required. The main obstacle is that all reagents, catalysts and intermediate species must tolerate their simultaneous presence. They must only interact in the desired step, without undergoing side reactions with any of the other compounds present. This is the main difference with respect to non single-operational one-pot strategies, in which reagents and intermediates do not need to tolerate each other, as they can be added at different points of the procedure.

Domino reactions not only provide a greener approach but also reduce the operational time, simplifying the experimental procedure. Recently, they have often been used in asymmetric

catalytic procedures for synthesizing enantiomerically pure intermediates with high-added value. Being able to obtain such compounds in a simple, straightforward manner is crucial. In many cases, such as the development of drug components in the pharmaceutical industry, only one of the enantiomers shows the desired properties. Thus, the enantiomeric purity determines the efficacy and selectivity of the drug. [7]

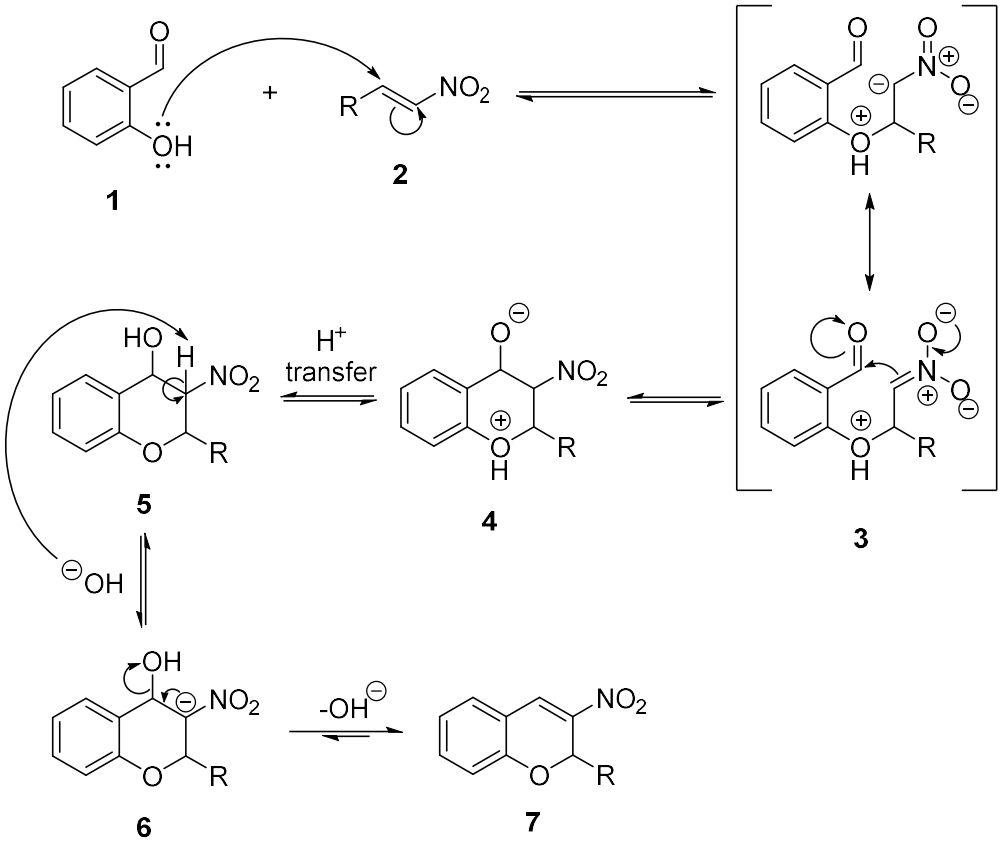
A highly interesting application of domino reactions is their use for synthesizing chromene derivatives through asymmetric catalysis. Chromenes are *O*-heterocyclic compounds with extraordinary biological and pharmacological properties. [3] Furthermore, they are useful building blocks for synthesizing high-added value heterocyclic compounds with antitumor, antiviral, antimicrobial and anticoagulant properties. [7] In particular, 3-nitro-2*H*-chromenes are high-value compounds, with a wide application range in chemistry and biology. Thus, 3-nitro-2*H*-chromene derivatives are valuable as synthetic intermediates and also used in light devices, pesticides and pharmacology, emphasizing their relevance as strong antitumor agents in this last application. [8]

An interesting example of the high versatility of 3-nitro-2*H*-chromenes as building blocks is their use for synthesizing chromene derivatives bearing 1,2,3-triazole rings. Triazoles, defined as five member heterocyclic compounds bearing three consecutive nitrogen atoms, are useful building blocks in the preparation of drugs with outstanding biological characteristics in terms of antitumor, antiviral, antibacterial and anti-inflammatory properties. [9] Furthermore, their aromaticity provides high resistance to oxidation, reduction and hydrolysis in acidic and basic conditions. Therefore, the combination of the chromene core with the 1,2,3-triazole ring results in highly relevant compounds with many interesting biological properties. For example, flavonoid derived structures, which are characterized by their effective antitumor and antiseizure activity. [10]

Traditionally, 1,2,3-triazoles were synthesized by Huisgen 1,3-dipolar cycloaddition between alkynes and azides, catalyzed by copper or ruthenium [9, 11]. However, both approaches have important drawbacks. The copper catalyzed processes only work properly for terminal alkynes and the ruthenium catalyzed processes need highly expensive ruthenium salts. Nevertheless, these problems can be surpassed by using nitro-olefin systems, such as 3-nitro-2*H*-chromenes, as building blocks. From these derivatives, 1,2,3-triazoles are easily available through an eliminative azide-olefin cycloaddition. For the synthesis of the starting 3-nitro-2*H*-chromenes, the most widespread approach is through the oxa-Michael Henry domino reaction of β-nitrostyrenes and salicylaldehydes. [8]

## 1.1. State of the art in asymmetric catalyzed oxa-Michael Henry domino reaction for the synthesis of 3-nitro-2*H*-chromenes

The first step of this process is the nucleophilic attack of the oxygen of salicylaldehyde to the nitro-olefin acceptor system. Then, the resulting nitronate **3** reacts *in situ* with the aldehyde function by the means of a Henry reaction, as shown in Scheme 1. [3]

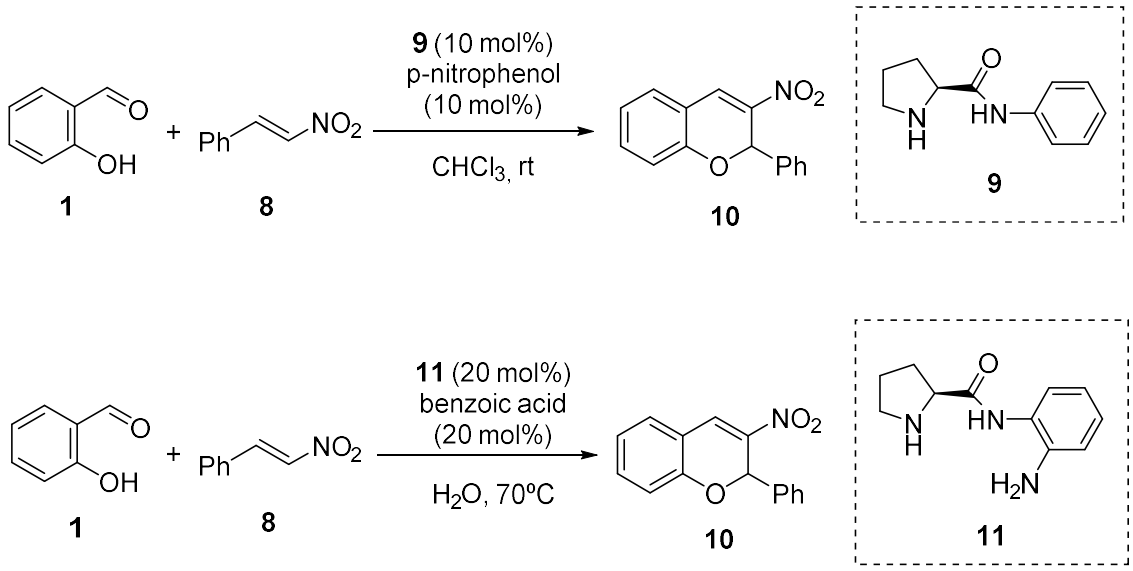



**Scheme 1.** Mechanism of the oxa-Michael Henry domino reaction between salicylaldehyde and nitro-olefin systems.

There are several examples of asymmetric oxa-Michael Henry domino reaction between β-nitrostyrenes and salicylaldehydes. However, the reaction usually performs poorly, mainly due to the poor nucleophilicity of the oxygen atom. [7] Therefore, most synthetic strategies require non-environmentally friendly organic solvents and long reaction times to achieve good yields.

The most common protocol for the asymmetric oxa-Michael Henry domino reaction for obtaining chiral 3-nitro-2-phenyl-2*H*-chromene employs L-proline derivatives as catalysts; two recent examples are depicted in Scheme 2. The first example, reported by Mohanta and Bez, is based on the use of phenyl L-prolinamide **9** as chiral catalyst, *p*-nitrophenol as co-catalyst and chloroform as solvent. [7] On the other hand, the second approach, described by Rani *et*

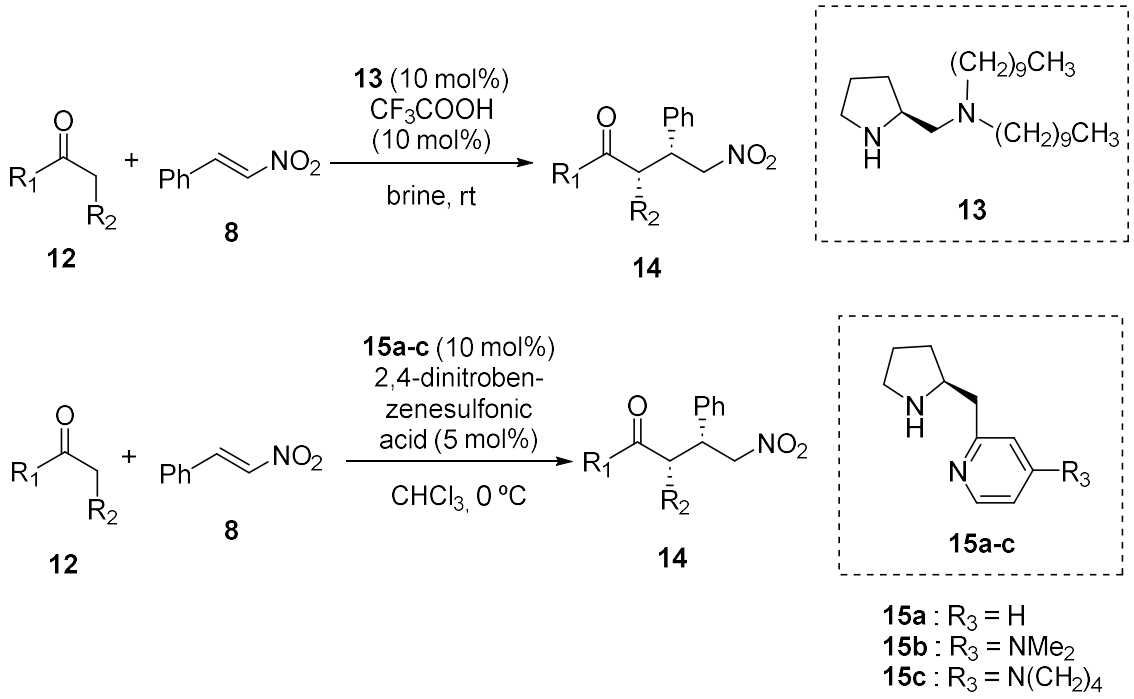
*al*., uses L-prolinamide derivative **11** as catalyst, benzoic acid as co-catalyst and water as solvent. [3] Salicylaldehyde and *trans*-β-nitrostyrene are used as starting reagents.




**Scheme 2.** Synthetic routes using L-proline derived catalysts.

Both approaches use cheap and highly available co-catalysts and provide excellent yields, especially the first approach (yield above 99%, whereas the other reaches 96%). The second route uses water as solvent, so it provides a greener approach, and requires lower reaction times (between 10 and 20 hours, whereas the other needs between 36 and 48 hours). However, the aqueous approach requires higher temperatures (70 °C), while the other works at room temperature. Moreover, if directly purchased, catalyst **9** is much cheaper than catalyst **11**. This last could also be synthesized in the laboratory following the protocol described by Rani *et al*. [3] and it does not require any especially expensive reagent. However, it demands very long reaction times. Finally, the synthetic route using chloroform shows high enantioselectivity, whereas the aqueous approach does not. Nevertheless, in this investigation project, we are not aiming at the synthesis of enantiopure derivatives, so enantioselectivity is not considered when analyzing the performance of the strategies.

Kotsuki *et al*. [12] compile in their review different synthetic strategies for performing asymmetric catalyzed Michael additions using other L-proline derived catalysts. The two most interesting approaches are compiled in Scheme 3.




**Scheme 3.** Asymmetric catalyzed Michael additions using L-proline derivatives

Both provide outstanding enantioselectivity, diastereoselectivity and yield (*ee* up to 97%, d.r. up to 98:2 and yield up to 99% for the first route and *ee* up to 99%, d.r. up to more than 99:1 and yield up to more than 99% for the second one). However, they have quite long reaction times (between 24 and 48 hours for both). [13, 14]

Although the described routes were applied for performing asymmetric catalyzed Michael addition, they could also be employed for performing asymmetric catalyzed oxa-Michael Henry domino reactions. Mohanta and Bez [7] studied the use of a tertiary amine L-proline derived catalyst to perform oxa-Michael Henry domino reaction (following the first approach of Scheme 2 but with this catalyst instead of catalyst **9**). This tertiary amine catalyst interacted, through the secondary amine of the pyrrolic ring part, with the carbonyl of salicylaldehyde, forming an iminium ion. In this way, the carbon atom gets more electrophilic, favoring the reaction with the nitro-olefin system. The difference with respect to catalyst **9** is that the secondary amide of this last was able to establish hydrogen bonding with the nitro group. This allowed stabilizing the intermediate and activating the nitroalkene in such a way Si-face attack was favored, as described in Figure 1.

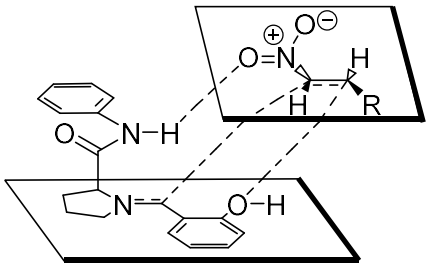
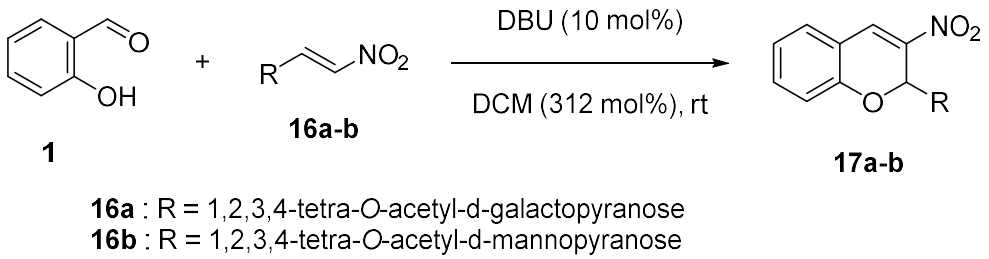


**Figure 1.** Intermediate stabilization through hydrogen bonding for a secondary amide catalyst.

On the other hand, the tertiary amine catalyst cannot develop such hydrogen bonding, so it proceeded with a very low enantioselectivity (*ee* of 5%). Nevertheless, very good yield (91%) was achieved. As previously said, in this investigation project enantioselectivity is not considered, so the only drawbacks of this experimental protocol are the long reaction times (5 days). [7] Going back to Scheme 3, knowing these catalysts and synthetic conditions work so well for asymmetric Michael addition and since tertiary amine L-proline derivative catalysts can also be used for oxa-Michael Henry domino reaction, it would be really interesting to try these approaches for studying their feasibility for oxa-Michael Henry domino reaction and observing if they proceed as expected in those new conditions. Especially, the first route is highly relevant because it works at room temperature and uses brine as solvent, making it an even greener approach. However, both routes share the same major drawbacks. The catalysts have very low availability and are extremely expensive if directly purchased. They could be synthesized in the laboratory, following the procedure described by Asami for catalyst **13**, [15] and that described by Ishii *et al*. for catalysts **15a**-**c**. [14]

Finally, the synthetic strategy designed by Luque-Agudo *et al*. was analyzed. [8] This approach, described in Scheme 4, is different from all previously studied in this investigation project. It uses the highly available and cheap DBU catalyst instead of an L-proline derived compound. Furthermore, on contrary to the routes described in Scheme 2 and Scheme 3, this other approach does not require any co-catalyst, works at room temperature and the reaction time is much shorter (below 2 hours). Considering all these features, the protocol is highly advantageous in terms of the development of greener processes: domino reaction (improving atom economy and allowing simple experimental procedure), no heating or cooling (decreasing the energy consumption), no co-catalyst (better atom economy) and although the used solvent doesn't belong to the category of green, it is added in small amounts.



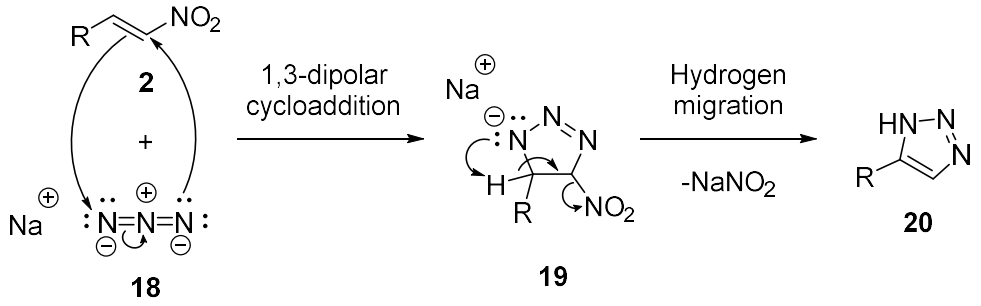

**Scheme 4.** Synthetic route using DBU catalyst**.**

The process was initially designed for carbohydrate derived β-nitroalkenes **16a**-**b** but it can also be expected to be effective with other β-nitroalkenes, such as aromatic derivatives. Even though the yields obtained following this procedure are moderate (around 30%), its experimental simplicity is a remarkable advantage.

Thus, an approach based on the synthetic strategy presented in Scheme 4 is chosen to perform the asymmetric catalyzed oxa-Michael Henry domino reaction between salicylaldehyde and *trans*-β-nitrostyrene.

## 1.2. State of the art in the eliminative azide-olefin cycloaddition for the synthesis of chromene derived 1,2,3-triazoles

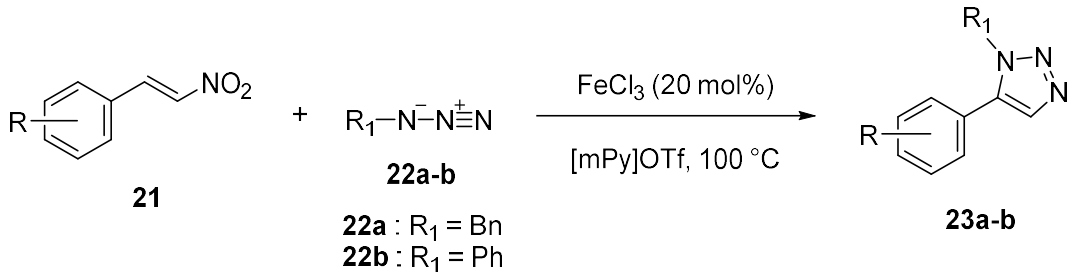
In the eliminative azide-olefin cycloaddition, the nitroalkene **2** reacts with sodium azide by the means of a 1,3-dipolar cycloaddition, forming the unstable 1,2,3-triazolide intermediate **19**. This last compound undergoes an elimination reaction and hydrogen migration, releasing sodium nitrite and forming the stable triazole product **20**, as depicted in Scheme 5. [9, 16]




**Scheme 5.** Eliminative azide-olefin cycloaddition of nitroalkenes and sodium azide.

Quan *et al.* reported that Brønsted and Lewis acids cause a relevant increase in the efficiency of the eliminative azide-olefin cycloaddition. [11] In this regard, De Nino *et al.* described a novel synthetic approach for the eliminative azide-olefin cycloaddition, based on the use of $FeCl_3$ in ionic liquid as catalytic system. [9] *Trans*-β-nitrostyrenes **21** react with azides **22a**-**b** in

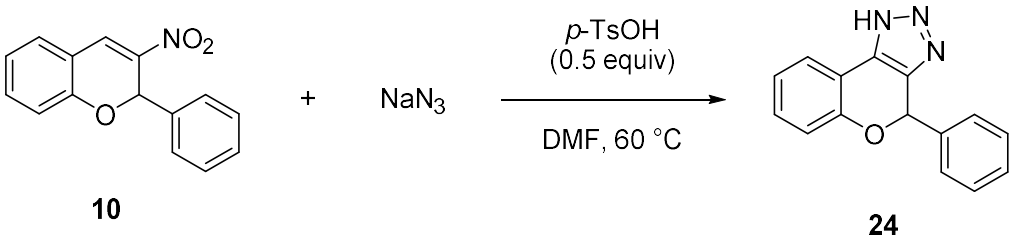
1-methyl pyridinium trifluoromethanesulfonate ([mpy]OTf) solvent and in the presence of $FeCl_3$ catalyst at 100 °C for 2 hours to afford the 1,2,3-triazoles **23a**-**b**, as shown in Scheme 6.




**Scheme 6.** Synthetic route using iron catalyst in ionic liquid solvent**.**

This protocol has been described for alkyl azides. Nevertheless, it could be expected to work properly for sodium azide. This procedure provides excellent yields (95% for **22a** and 91% for **22b**) with short reaction times. Iron catalysts are quite cheap and do not cause any remarkable environmental impact. Moreover, ionic liquids can be easily recovered along with the catalyst, so the catalytic system can be recycled. According to the results obtained by De Nino *et al.* [9], the ionic liquid/ $FeCl_3$ catalytic system can be efficiently recovered and reused in six reaction cycles with very little decrease in yield. These are excellent outcomes in terms of Green Chemistry as they imply a relevant decrease in the amount of solvent and catalyst required. However, the major drawback of this procedure is the risk implied. Lewis acids enhance the explosive nature of azides, even more so when heated. Thus, the addition of $FeCl_3$ must be cautiously performed under the proper safety measures. Moreover, there is another drawback to take into account, which is the cost associated to the synthesis of the ionic liquid, in terms of reagents and time. Following the procedure described by Bortolini *et al.*, the production of [mpy]OTf is quite time consuming and the required methyl trifluoromethanesulfonate is not especially cheap. [17]

Alternatively, Quan *et al.* used *p*-toluenesulfonic acid as catalyst for the eliminative azide-olefin cycloaddition of the nitro-olefin **10** with sodium azide in DMF at 60 °C, to obtain the triazole **24** in an excellent 95% yield, as described in Scheme 7. [11]

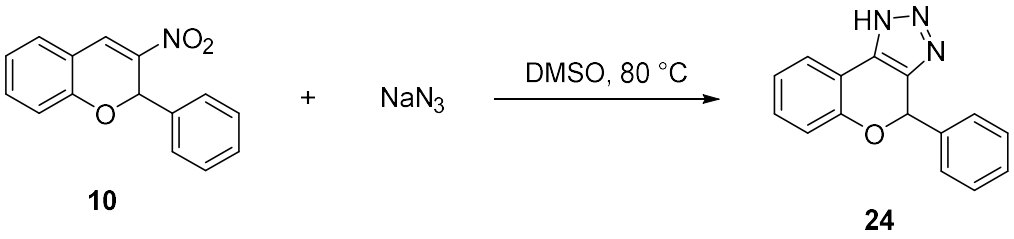



**Scheme 7.** Synthetic route using *p*-toluenesulfonic acid catalyst and DMF solvent.

The main drawback of this procedure is again the operational risks involved. Brønsted acids have to be carefully handled when mixed with sodium azide, due to the toxic and explosive character of hydrazoic acids that may be formed. Therefore, the addition of *p*-toluenesulfonic acid must be cautiously performed under the proper safety measures. Furthermore, in terms of Green Chemistry, it is not an ideal approach, since it requires DMF, a hazardous solvent restricted by the European Chemicals Agency. [18] Therefore, the environmental impact of this procedure cannot be neglected.

To avoid all these risks associated to the use of Brønsted or Lewis acid catalysts, the reaction could be done in the absence of any catalyst. Under these conditions, not only higher temperatures and longer reaction times are usually required but also regioselectivity and yields are lower. [9, 11] Therefore, when Quan *et al.* tried this approach for *trans*-β-nitrostyrene, they observed a significant decrease in yield, which lowered to 30% and higher temperature (110 °C) was required. [11]

However, when Habib *et al.* employed 3-nitrochromenes as starting materials, the reaction was done at 80 °C for just 25 minutes to afford the desired triazole **24** in a 79% yield, as depicted in Scheme 8. [19]




**Scheme 8.** Synthetic route using no catalyst and DMSO solvent.

This last approach combines a decrease in operational risk with lower environmental impact, simple reaction conditions, high efficiency and good atom economy (as the reaction is catalyst

free). Thus, due to all this advantages, a procedure based on Scheme 8 will be used to perform the eliminative azide-olefin cycloaddition between the 3-nitrochromene **10** and sodium azide.

# 2 Objectives

3-Nitro-2*H*-chromenes and chromene derived 1,2,3-triazoles have exceptionally useful properties and applications, among which their use as valuable building blocks for synthesizing high-added value heterocyclic compounds in the pharmaceutical industry stands out. This research project focuses on analyzing the asymmetric catalyzed oxa-Michael Henry domino reaction and the eliminative azide-olefin cycloaddition. Several synthetic strategies, described in the literature, are compared considering yield, time, number of steps and use of affordable equipment and reagents while seeking for the least environmental impact, following the principles of Green Chemistry.

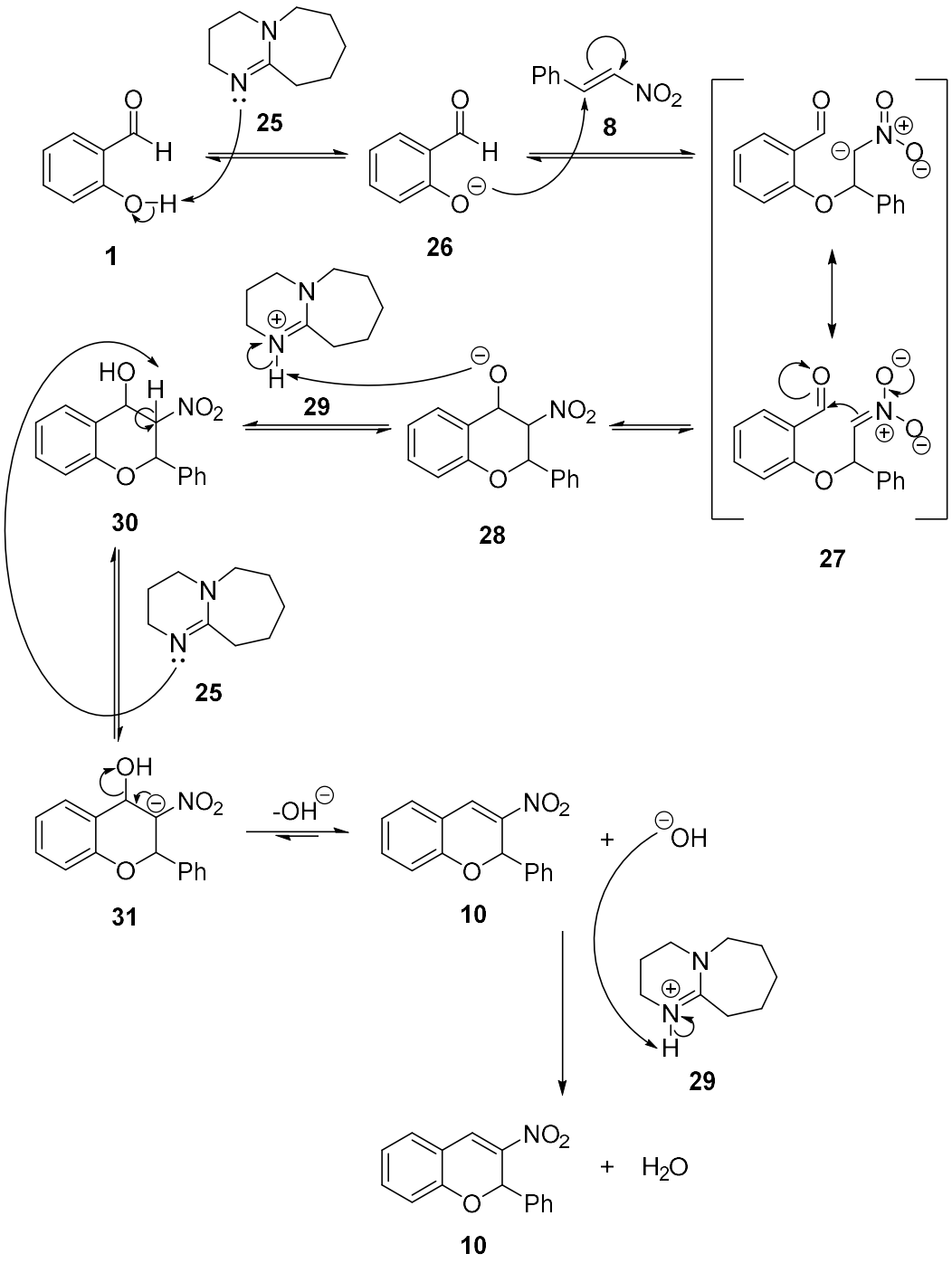
The most suitable options are experimentally studied. The oxa-Michael Henry domino reaction is analyzed through the reaction of salicylaldehyde with *trans*-β-nitrostyrene, obtaining 3-nitro-2-phenyl-2*H*-chromene. On the other hand, the eliminative azide-olefin cycloaddition is analyzed through the reaction of 3-nitro-2-phenyl-2*H*-chromene with sodium azide, isolating 4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]triazole.

# 3 Results and discussion

In this section, the employed procedures are interpreted in detail, keeping special attention to the mechanisms, intermediates and byproducts formation, yields and product characterization through NMR spectroscopy. In addition, all the difficulties and problems faced are described, as well as the reasoning behind the results obtained and possible improvements.

The reaction of salicylaldehyde with *trans*-β-nitrostyrene catalyzed by DBU follows the general mechanism described in Scheme 9. The oxa-Michael Henry reaction gives intermediate **30**, which undergoes dehydration, giving the 3-nitrochromene **10**. The role of DBU catalyst is to act as a base, forming the alkoxide **26** that is able to attack the nitroalkene **8**. The resulting nitronate **27** reacts *in situ* with the aldehyde function. Then, the protonated DBU **29** gets deprotonated, recovering the catalyst and forming the intermediate **30**. DBU acts again as a base, deprotonating the intermediate **30**, which releases a hydroxide anion. Finally, that hydroxide reacts with the protonated DBU **29** formed in the previous step, recovering the catalyst and forming the 3-nitrochromene **10**. The formation of a highly conjugated system and

the reaction of the hydroxide with the protonated DBU **29** favor the dehydration of the intermediate **30**, driving the mechanism towards product formation. Moreover, DBU is a proper catalyst because it is a non nucleophilic base. In case a nucleophilic base was used, there would be undesired byproducts due to the nucleophilic attack of that base to the nitroalkene **8**.




**Scheme 9.** Mechanism for the formation of chromene **10** from salicylaldehyde and *trans*-β-nitrostyrene.

After 24 h, the $^{1}$H NMR of the crude reaction mixture (Figure 2) shows two signals in the aldehyde region: some unreacted salicylaldehyde at 10.05 ppm and the aldehyde intermediate **32** from the Michael addition at 9.96 ppm. The mechanism for the formation of compound **32** is depicted in Scheme 10. The signal at 8.08 ppm corresponds to the desired 3-nitrochromene **10**, indicating that the conversion is moderate, as the ratio **32**/**10** is 2:1.

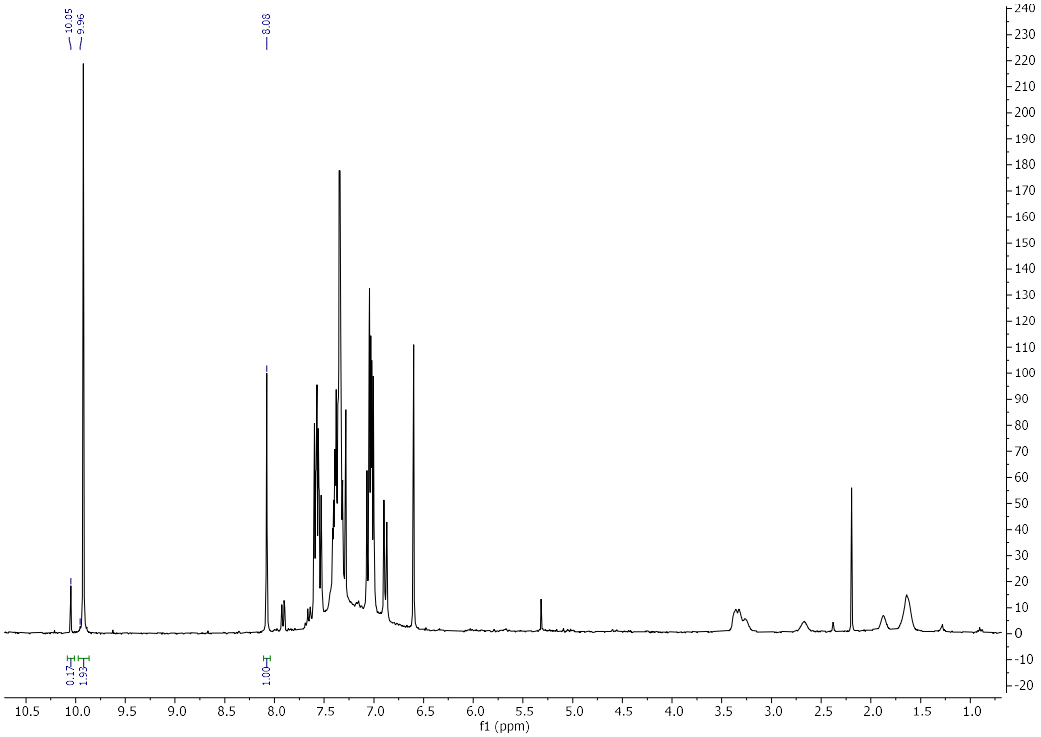
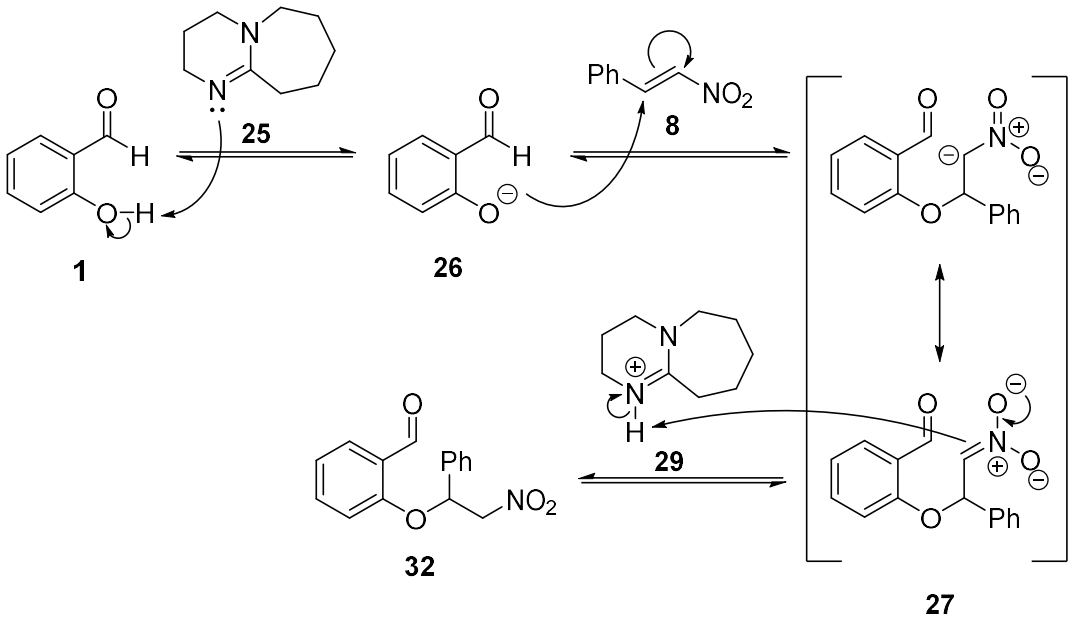



**Figure 2.** $^{1}$H NMR spectrum of the crude reaction mixture of the DBU-catalyzed reaction of salicylaldehyde and trans-β-nitrostyrene (300 MHz with $CDCl_3$).

Purification of the crude reaction mixture by flash chromatography afforded a fraction of pure 3-nitrochromene **10** and a fraction of a mixture of aldehyde **32** and 3-nitrochromene **10**, from which pure 3-nitrochromene **10** was isolated by crystallization in isopropanol. The combined yield of desired 3-nitrochromene is 6%.

3-Nitro-2-penyl-2*H*-chromene **10** was fully characterized by $^{1}$H NMR, $^{13}$C {$^{1}$H}-NMR, DEPT-135 and IR. Thus, the $^{1}$H NMR spectrum (Figure 3) displays a singlet at 6.60 ppm integrating for 1 H, which corresponds to the hydrogen attached to C 8, highly deshielded because it is in a benzylic position and close to the oxygen. The doublet at 6.89 ppm, the triplet at 7.02 ppm and the multiplet between 7.32-7.41 ppm correspond to the aromatic hydrogens, since when combined they integrate for 9 H. Considering the multiplicity and the integration, the doublet corresponds to the H attached to C 6 or 3 and the triplet to the H of C 1 or 2, as in both cases

the signal integrates for 1 H and they couple with an *ortho* hydrogen in the case of the doublet and with two *ortho* hydrogens in the case of the triplet.




**Scheme 10.** Formation of the aldehyde **32** byproduct.

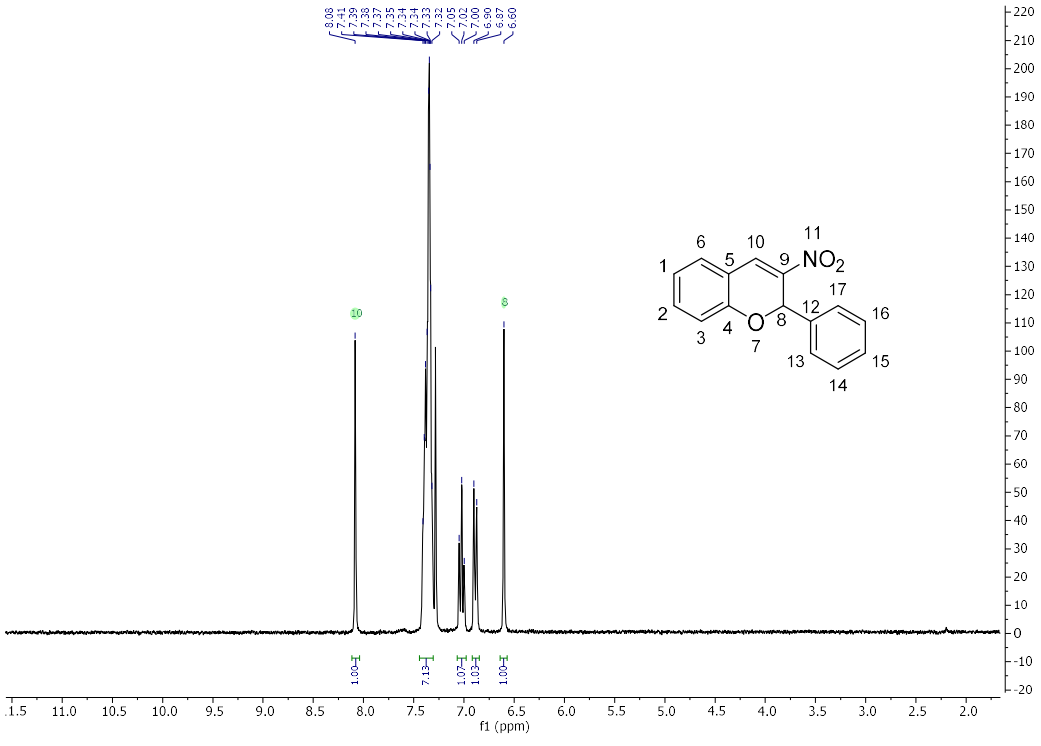



**Figure 3.** $^{1}$H NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene **10** (300 MHz, $CDCl_3$).

This coupling can be confirmed by calculating the values of the coupling constants (*J*). The doublet has a $^{3}J$ = 8.5 Hz and the triplet shows a $^{3}J$ = 7.5 Hz. These values follow the expected

behavior for *ortho* hydrogens in a benzene ring ($^3J_{ortho}$ = 6-9.5 Hz). [22] The 5 hydrogens of the phenyl group and the two other aromatic hydrogens remaining give the multiplet that integrates for 7 H. Finally, the most deshielded signal, at 8.08 ppm, is a singlet integrating for 1 H. It corresponds to the H attached to C 10. It is highly deshielded because it belongs to an alkene group and at the same time it is in a benzylic position and relatively close to the electron withdrawing nitro group.

Analysis of the $^{13}C$ {$^1H$}-NMR and DEPT-135, shown in Figure 4 and Figure 5, respectively, further confirmed the formation of the desired 3-nitrochromene **10**. Thus, the signal at 153.6 ppm corresponds to C 4. Since it is quaternary there is no signal in the DEPT-135 spectrum and it is the most deshielded due to the electron withdrawing effect of the adjacent oxygen. The other signals that do not appear in Figure 5 correspond to the ipso carbons of the molecule, at 141.3, 136.9 and 118.0 ppm.

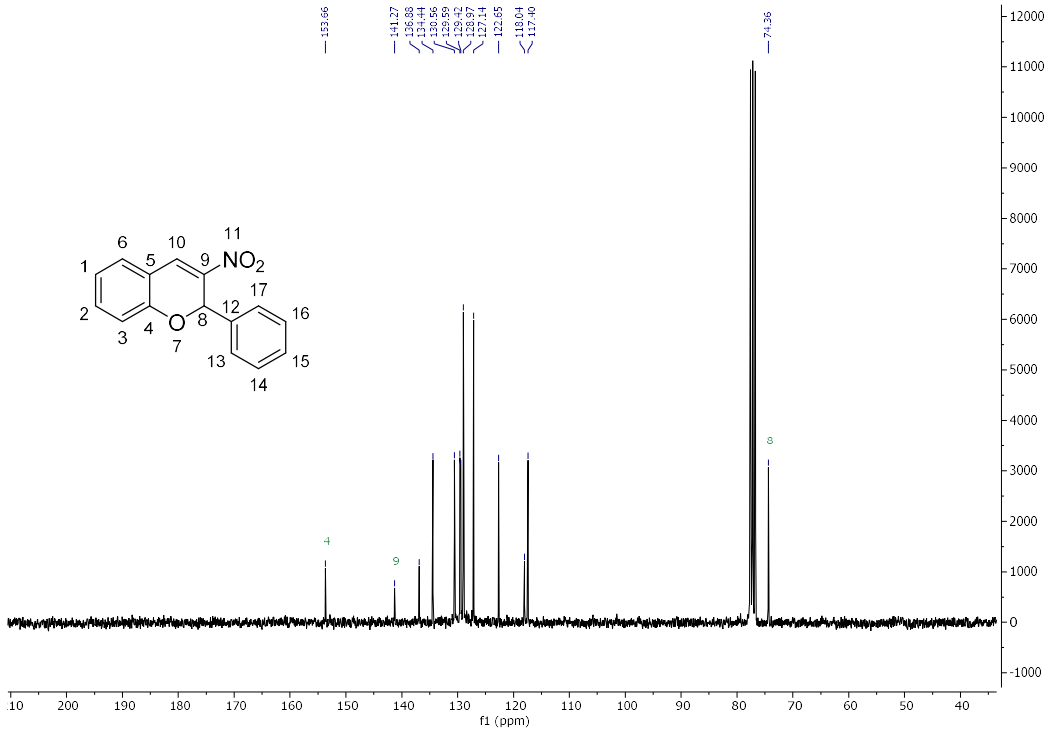



**Figure 4.** $^{13}C$ {$^1H$}-NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene **10** at 75 MHz using $CDCl_3$ solvent.

The one at 141.3 ppm belongs to the quaternary carbon attached to the nitro group. It is the most deshielded of them due to the effect of the adjacent electron withdrawing nitro group. The remaining signals in the region between 160 and 110 ppm correspond to the aromatic carbons and the other alkene carbon (C 10). Among them, the peaks at 129.0 and 127.1 ppm belong to the *ortho* and *meta* carbons of the phenyl group. The two *ortho* and *meta* carbons

are chemically equivalent due to symmetry, leading to more intense signals. The remaining signal at 74.4 ppm belongs to C 8. It is the most shielded peak as it is not an aromatic or an alkene carbon but even so it is quite deshielded due to the effect of the adjacent oxygen.

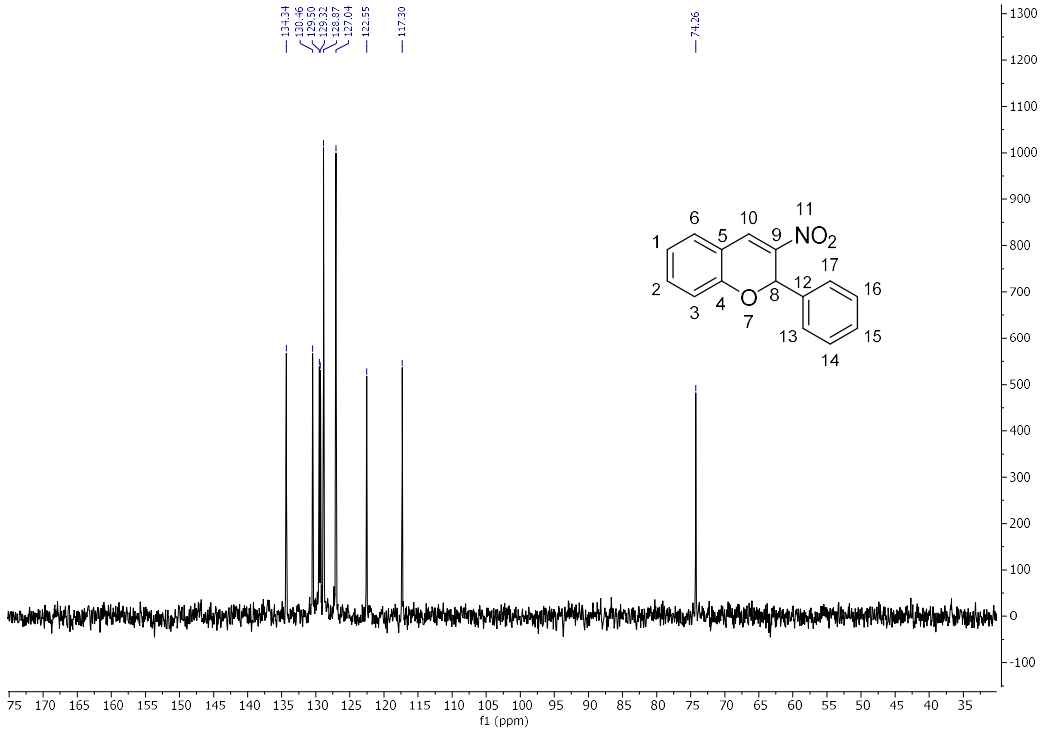



**Figure 5.** DEPT- 135 spectrum of 3-nitro-2-phenyl-2*H*-chromene **10** at 75 MHz using $CDCl_3$ solvent

The presence of the nitro group was confirmed by IR (Figure 6), displaying the characteristic bands corresponding to the symmetric and asymmetric stretching of the N-O bond of the nitro group at 1545.67, 1491.19, 1450.21 and 1318.59 $cm^{-1}$.

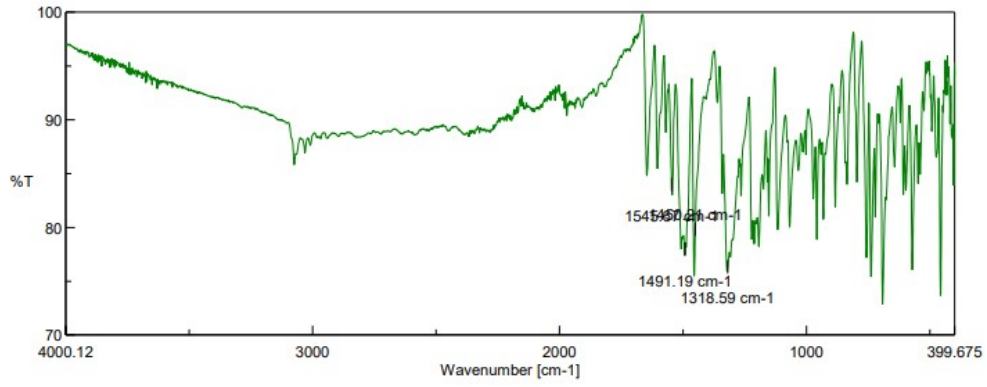


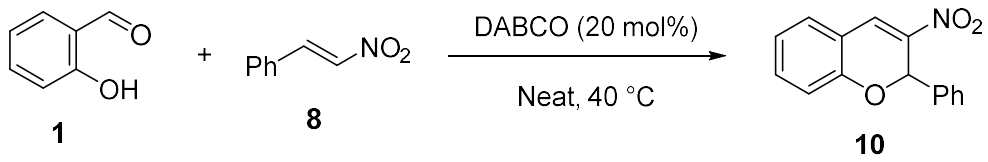

**Figure 6.** IR spectrum of chromene **10**.

The data are consistent with those reported in the literature, describing bands for the nitro group at 1544 and 1325 $cm^{-1}$, very close to our experimentally observed bands at 1545.67 and

1318.59 $cm^{-1}$. [7] The melting point for 3-nitrochromene **10** (103-104 °C) indicates high purity and is consistent with the value reported in the literature (92-93°C). [7]

Despite affording the desired 3-nitrochromene **10**, the low yield encouraged us to investigate further and search the literature for alternative synthetic procedures. A solvent-free procedure using DABCO as catalyst independently reported by Baral *et al.* and Yao *et al.* caught our attention. [20, 21] As DABCO is also a non nucleophilic base, the mechanism would be analogous to the reaction with DBU. The procedure is relatively fast (1-3 hours), does not require any co-catalyst and, despite heating is required (40 °C), the energy consumption is low. Therefore, this is an optimal approach in terms of Green Chemistry.

Baral *et al.* employed 1.0 equiv of both reagents and 0.2 equiv of the catalyst, obtaining yields between 83% and 94%. [20] On the other hand, Yao *et al.* used 1.0 equiv of *trans*-β-nitrostyrene, 3.0 equiv of salicylaldehyde and 0.5 equiv of DABCO, obtaining 98% yield. [21] Both provide excellent yields but the approach employed by Baral *et al.* requires lower amounts of reagents and catalyst, improving even more the atom economy of the procedure. [20] Thus, a synthetic strategy based on the procedure employed by Baral *et al.* was developed, following Scheme 11. [20] Moreover, when compared to the previously employed approach, it was expected to obtain much better yields (Luque-Agudo *et al*. achieved 30% yield using the DBU-catalyzed strategy, whereas Baral *et al.* achieved yields in the range of 83-94%). [8, 20]




**Scheme 11.** Solvent free synthetic route using DABCO catalyst**.**

So we decided to investigate the DABCO-catalyzed formation of 3-nitrochromene **10** under neat conditions. The analysis of the crude reaction mixture by $^{1}H$ NMR (Figure 7) showed a ratio 3-nitrochromene **10**/salicylaldehyde **1**/aldehyde **32** of 76/4/20, indicating a much better conversion when compared with the DBU-catalyzed reaction.

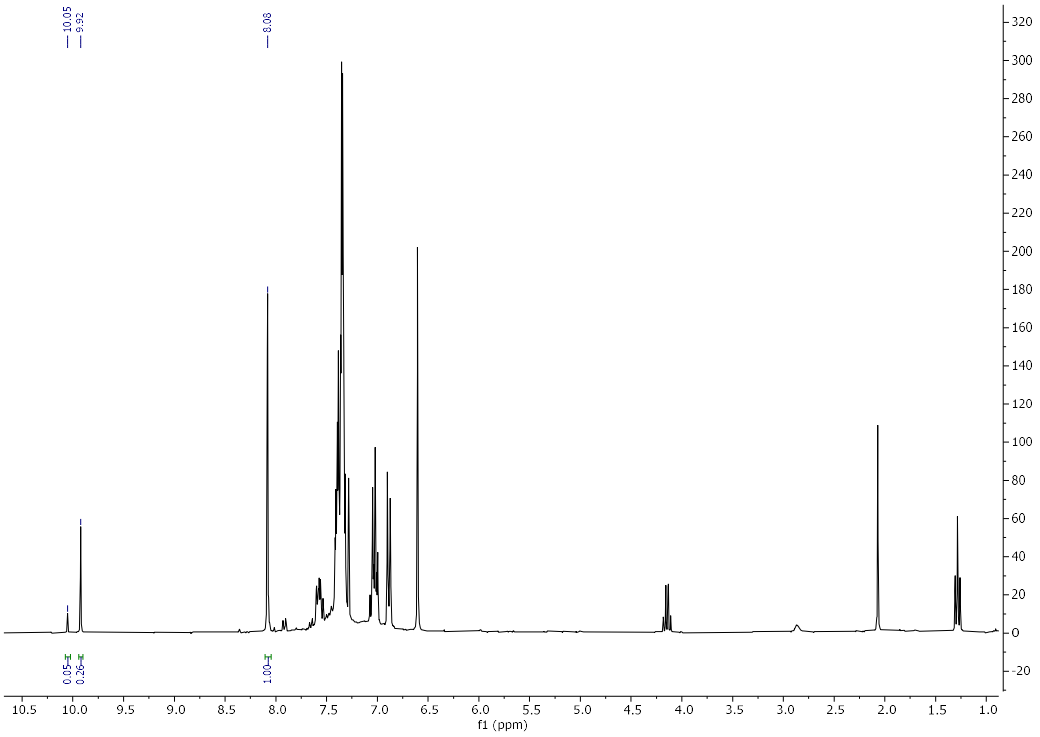
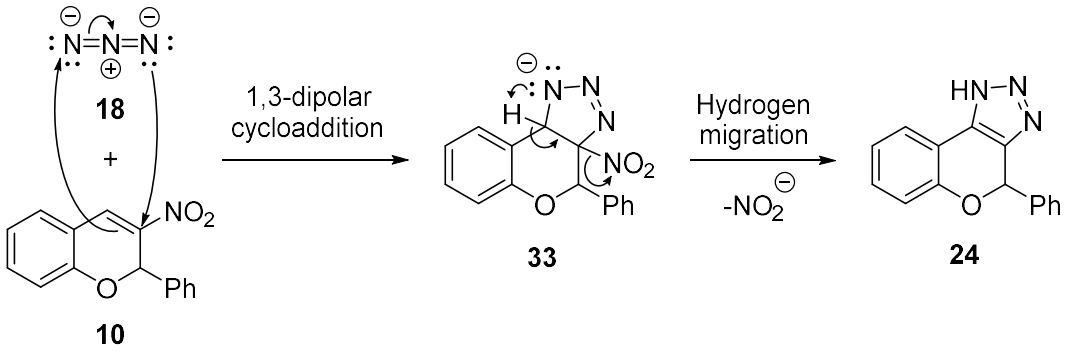



**Figure 7.** $^{1}$H NMR spectrum of the crude reaction mixture of the DABCO-catalyzed reaction of salicylaldehyde and *trans*-β-nitrostyrene (300 MHz, $CDCl_3$).

Unfortunately, some product was lost during the purification step. As a consequence, a comparison of the isolated yields using both procedures was not possible. Even so, the obtained yield (13%) is larger than when using the DBU-catalyzed approach.

Once the 3-nitrochromene **10** was obtained, it was used as starting material to perform the one step eliminative azide-olefin cycloaddition with sodium azide, following the mechanism described in Scheme 12, to obtain the 1,2,3-triazole **24**. Thus, 3-nitrocrhromene **10** reacts with sodium azide through a 1,3-dipolar cycloaddition, forming the unstable triazolide intermediate **33**, which readily gives the triazole **24** via hydrogen migration. [16] Habib *et al.* characterized the structure of the triazole **24** through single crystal X-ray diffraction analysis. According to it, the NH group of the triazole ring is oriented towards the benzene ring of the 3-nitrochromene. They proposed that the regioselectivity of the reaction may be caused by the steric effect of the phenyl group. [19] The negatively charged nitrogen has two lone electron pairs that would undergo higher steric hindrance with the phenyl group if the nitrogen close to it was negatively charged. Therefore, the resonance structure depicted in Scheme 12 for the triazolide **33** intermediate predominates, favoring hydrogen migration to the nitrogen oriented towards the benzene ring.




**Scheme 12.** Mechanism for the formation of 1,2,3-triazole **24** from chromene **10** and sodium azide.

After completion of the reaction (3.5 h, see appendix 2) and quenching with water, insoluble triazole **24** precipitated from the reaction mixture. However, isolation of this solid by filtration was not possible, so a liquid-liquid extraction protocol was performed as an alternative. The crude product was then purified by flash chromatography, affording the triazole **24** as a pale brown solid (see appendix 1).

The purified product was characterized by $^{1}$H NMR, $^{13}$C {$^{1}$H}-NMR and DEPT-135 (Figure 8, Figure 9 and Figure 10). The signals of the 1,2,3-triazole **24** can be easily assigned and the data match with those reported in the literature (see appendix 6 and 7).

The $^{1}$H NMR displays a signal at 6.62 ppm corresponding to the hydrogen attached to C 8 as it is a singlet integrating for 1 H. It is highly deshielded because it is in a benzylic position and close to the oxygen. The remaining signals, integrating for 9 H when combined, belong to the aromatic hydrogens. The most deshielded signal, at 7.82 ppm, corresponds to one of the *ortho* hydrogens of the benzene ring of the chromene (that attached to C 3 or C 6). It is a doublet so it can only correspond to the *ortho* hydrogens of the benzene rings. The other hydrogens would have higher multiplicity. Moreover, the signal integrates for 1 H, what discards the *ortho* hydrogens of the phenyl group. These last should give a signal integrating for 2 H since they are chemically equivalent due to symmetry. Taking into account these ideas, the doublet at 7.10 ppm that integrates for 2 H has to belong to the *ortho* hydrogens of the phenyl group (those attached to C 15 and C 19). In addition, the roof effect is observed due to the closeness in chemical shifts for the signals in the aromatic region. This also indicates a strong coupling between the aromatic protons. The coupling of the two doublet signals can be checked by analyzing their *J*, which is $^{3}J$ = 7.6 Hz for both. The obtained values follow the expected behavior for *ortho* hydrogens in a benzene ring ($^{3}J_{ortho}$ = 6-9.5 Hz) [22] thus supporting the previous assignment for these signals.

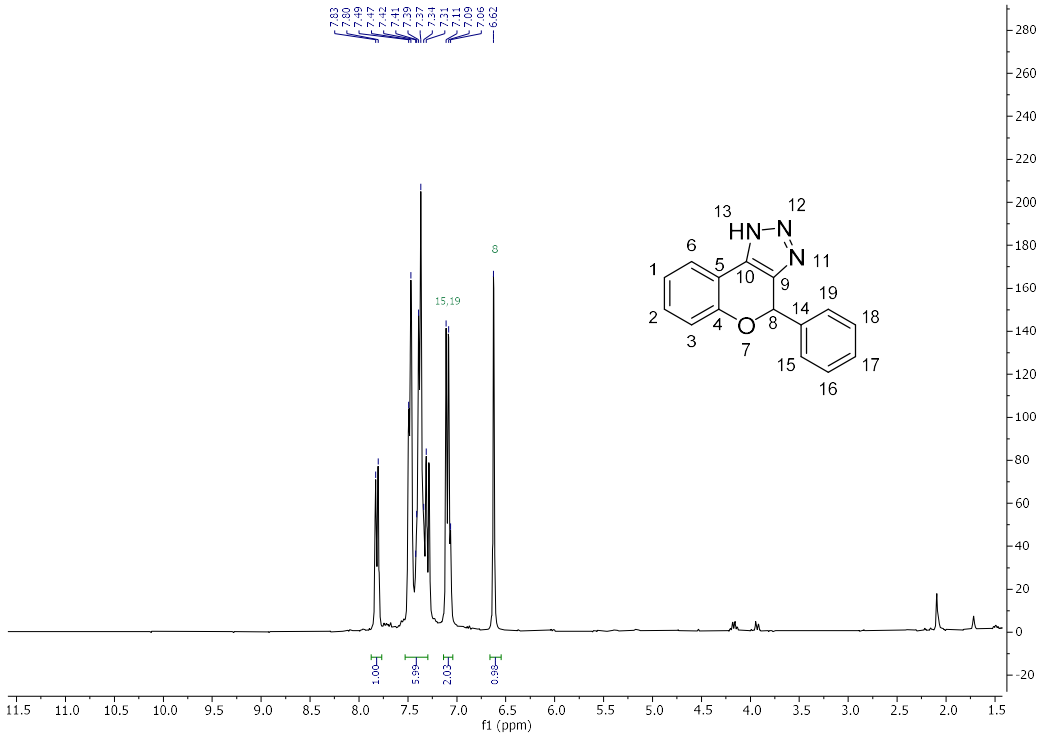



**Figure 8.** $^{1}$H NMR spectrum of 1,2,3-triazole **24** at 300 MHz using $CDCl_3$ solvent.

Regarding the $^{13}$C NMR, signals at 153.4, 142.0, 138.6, 138.5 and 115.6 ppm correspond to ipso carbons as they do not appear in the DEPT-135 spectrum. The most deshielded signal corresponds to C 4 due to the electron withdrawing effect of the adjacent oxygen. The signal at 142.0 ppm belongs to C 10. It is highly deshielded due to the inductive effect caused by the adjacent nitrogen. This effect is also present in C 9 but C 10 is more deshielded as it is closer to the aromatic ring. The signals at 138.6 and 138.5 ppm correspond to C 9 and C 5 and the peak at 115.6 ppm belongs to the ipso carbon of the phenyl group. The remaining signals in the region between 160 and 110 ppm correspond to the aromatic carbons. Among them, the peaks at 128.8 and 127.1 ppm belong to the *ortho* and *meta* carbons of the phenyl group. The two *ortho* and *meta* carbons are chemically equivalent due to symmetry, leading to more intense signals. The remaining signal at 76.1 ppm belongs to C 8. It is the most shielded peak as it is not an aromatic carbon, but even so it is quite deshielded due to the effect of the adjacent oxygen.

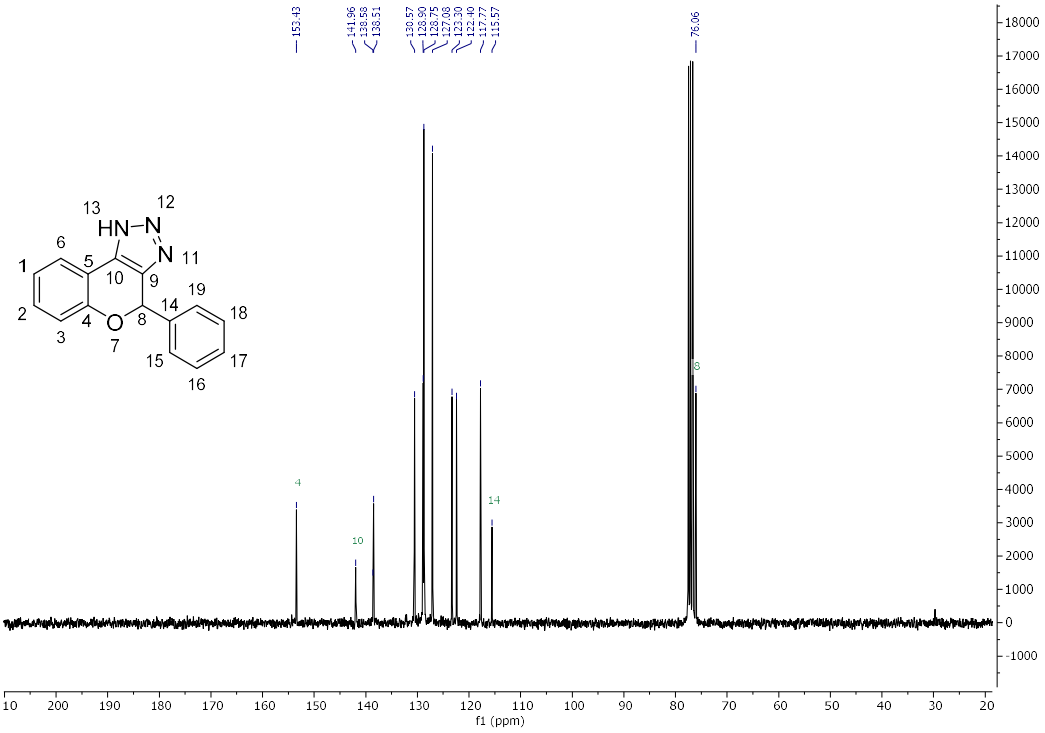



**Figure 9.** $^{13}C$ {$^{1}H$}-NMR spectrum of 1,2,3-triazole **24** at 75 MHz using $CDCl_3$ solvent.

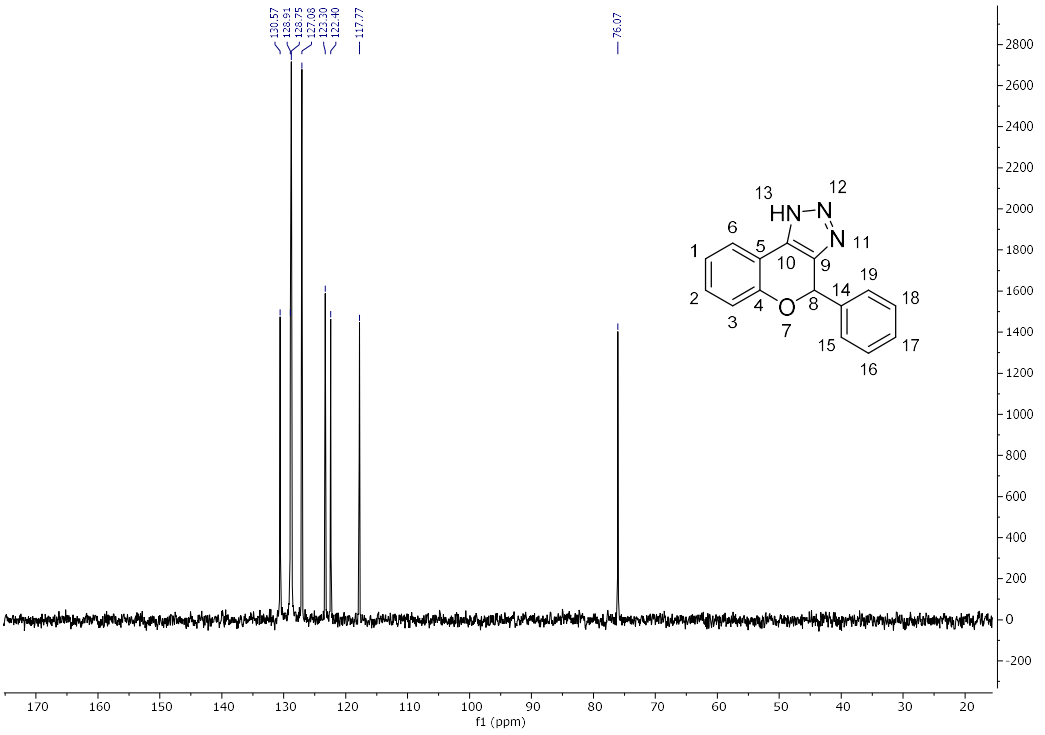



**Figure 10.** DEPT- 135 spectrum of 1,2,3-triazole **24** at 75 MHz using $CDCl_3$ solvent.

Although the employed procedure allowed the synthesis of the desired triazole **24** with high purity, the obtained yield was moderate (40%). Nevertheless, this value is in line with the

yields reported in the literature for similar systems, such as *trans*-β-nitrostyrene, under non-catalytic conditions. The eliminative azide-olefin cycloaddition also proceeds smoothly for other heterocyclic substituted or vinyl substituted nitro-olefins, such as 3-nitrocoumarins or acyclic α-carbethoxy-1-nitroalkenes but aliphatic nitro-olefins do not show any reactivity, not even when using catalytic conditions. [11, 16]

# 4 Conclusions

In this research project, the asymmetric catalyzed oxa-Michael Henry domino reaction for the preparation of 3-nitro-2*H*-chromenes was experimentally studied through the reaction of the commercially available salicylaldehyde with *trans*-β-nitrostyrene. The reaction was investigated using either DBU or DABCO as catalysts; both procedures allow the isolation of the desired product with high purity, but the DABCO-catalyzed one affords higher conversions and is solvent-free, so is more convenient from the point of view of sustainability.

The use of eliminative azide-olefin cycloaddition for synthesizing 1,2,3-triazoles was also studied. This strategy was experimentally analyzed through the reaction of the previously obtained 3-nitro-2-phenyl-2*H*-chromene with the commercially available sodium azide. The employed catalyst-free procedure not only implies little environmental impact, good atom economy and short reaction times but also allows isolating the product with high purity and moderate yields, making it a feasible alternative for synthesizing chromene derived 1,2,3-triazoles, such as 4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]-triazole.

The 3-nitro-2-phenyl-2*H*-chromene and 4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]triazole were fully characterized using $^{1}$H NMR and $^{13}$C {$^{1}$H}-NMR spectroscopy.

# 5 Experimental procedure

### General information

All the reactions were carried out in dried glassware with magnetic stirring. Although according to the employed references inert environment was not mandatory for any of the reactions, a nitrogen atmosphere was established to avoid any interference of water from moisture. Water is removed due its nucleophilic character, as it could attack the nitroalkene, competing with salicylaldehyde or sodium azide in their respective reactions. All the reagents and solvents were obtained from the commercial supplier and used without further purification. The

reagents used are DBU (≥98% purity), DABCO (≥99% purity) *trans*-β-nitrostyrene (98% purity), salicylaldehyde (98% purity) and sodium azide (≥99% purity). An oil bath was used for heating when required. All reactions were followed by TLC, which was performed using 0.2 mm precoated silica gel 60 $F_{254}$ aluminum sheets with visualization of the compounds under UV light. All $^{1}H$ NMR and $^{13}C$ {$^{1}H$}-NMR spectra were recorded on 300 MHz Bruker AV, using as reference $CDCl_3$ (7.28 ppm for $^{1}H$ NMR, 77.0 ppm for $^{13}C$ NMR). Data for $^{1}H$ NMR were reported including chemical shift (ppm) and multiplicity (s = singlet, d = doublet, t = triplet and m = multiplet) with the corresponding coupling constant (*J*) in Hertz (Hz). Data for $^{13}C$ NMR were reported giving the chemical shifts in ppm. The software employed for the spectroscopic analysis was MestreNova.

## Synthesis of 3-nitro-2-phenyl-2*H*-chromene

**Method A:** Salicylaldehyde (1.00 equiv, 15.00 mmol, 1.60 mL) was added to a yellow solution of *trans*-β-nitrostyrene (1.00 equiv, 15.00 mmol, 2.23 g) in DCM (6.00 mL). Then, DBU (0.20 equiv, 3.00 mmol, 0.44 mL) was added and the orange mixture was stirred until complete disappearance of the *trans*-β-nitrostyrene was observed by TLC (approx. 24 hours). The reaction mixture was diluted with DCM and filtered through a celite pad and the filtrate was washed with $H_2O$ and brine. The organic phase is dried over anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography ($SiO_2$, Hex to Hex/EtOAc 20:1) and then crystallization ($^{i}$PrOH), to afford the desired 3-nitrochromene **10** as an orange solid (0.23 g, 6% yield).

**Method B:** A mixture of salicylaldehyde (1.00 equiv, 15.00 mmol, 1.60 mL), *trans*-β-nitrostyrene (1.00 equiv, 15.00 mmol, 2.23 g) and DABCO (0.20 equiv, 3.00 mmol, 0.34 g) was stirred while heating at 40 °C until complete disappearance of the *trans*-β-nitrostyrene was observed by TLC (approx. 5 hours). The resulting mixture obtained was diluted with AcOEt and washed with water. The organic phase was dried over anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, Hex to Hex/EtOAc 20:1) to afford 3-nitrochromene **10** as an orange solid (442 mg, 13% yield).

**Mp:** 103-104 °C ($^{i}$PrOH)

**IR (neat)**: 1642.57, 1545.67, 1491.19, 1450.21, 1318.59, 1189.38, 1113.69, 1067.89 $cm^{-1}$.

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 8.08 (s, 1H), 7.44 – 7.30 (m, 7H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H).

**$^{13}$C {$^{1}$H}-NMR (75 MHz, $CDCl_3$):** δ 153.66, 141.27, 136.88, 134.44, 130.56, 129.59, 129.42, 128.97, 127.14, 122.65, 118.04, 117.40, 74.36.

### Synthesis of 4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]triazole

Sodium azide (2.00 equiv, 0.72 mmol, 0.05 g) was added to a solution of the previously isolated 3-nitrochromene **10** (1.00 equiv, 0.36 mmol, 0.09 g) in DMSO (1.10 mL) and the resulting mixture was stirred at 80 °C for 3.5 hours. (NOTE: Azides are explosive, so they must be handled with care). The reaction mixture was cooled down to room temperature, diluted with DCM and washed with $H_2O$ and brine. The organic phase was dried over anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, Hex/EtOAc 3:1) to afford desired triazole **24** as a pale brown solid (35 mg, 40% yield).

**$^{1}$H NMR (300 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.30 (m, 6H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.62 (s, 1H).

**$^{13}$C {$^{1}$H}-NMR (75 MHz, $CDCl_3$):** δ 153.43, 141.96, 138.58, 138.51, 130.57, 128.90, 128.75, 127.08, 123.30, 122.40, 117.77, 115.57, 76.06.

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# Appendixes

**Appendix 1:** pictures of the products obtained from the reactions: **(a)** 3-nitro-2-phenyl-2*H*-chromene **10** doing the DBU-catalyzed approach, **(b)** 3-nitro-2-phenyl-2*H*-chromene **10** doing the DABCO-catalyzed approach and **(c)** 4-phenyl-1,4-dihydrochromeno[3,4-d][1,2,3]triazole **24**.

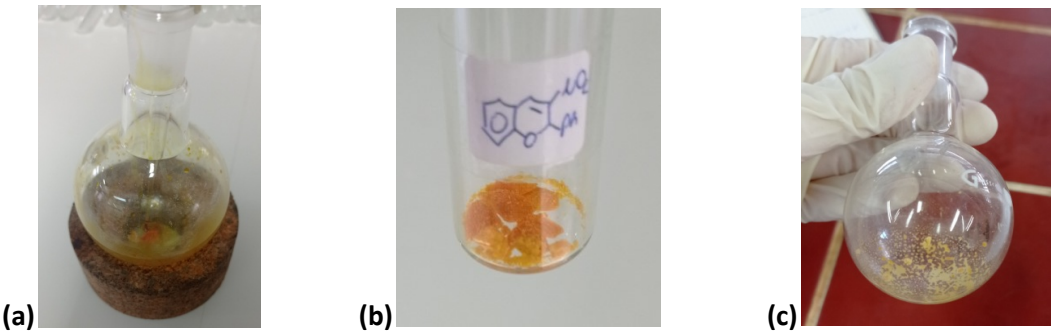

**Image 1.** Pictures of the products.

**Appendix 2:** TLC studies of the reaction mixtures for: **(a)** DBU-catalyzed approach after 24 hours, **(b)** DABCO-catalyzed approach after 5 hours and **(c)** triazole formation after 3.5 hours.

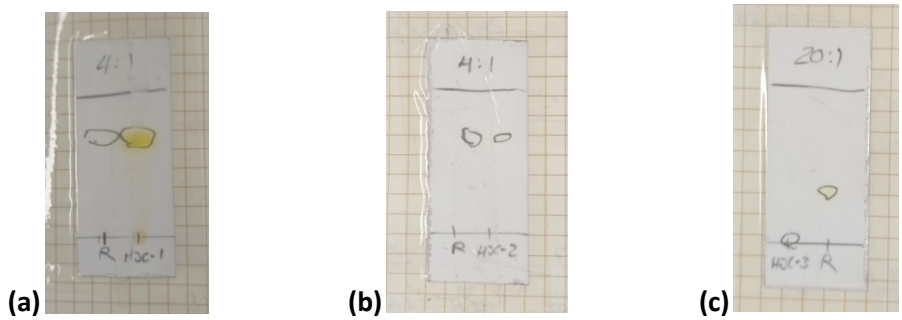

**Image 2.** TLC studies of the reaction mixtures.

**Appendix 3:** TLC study of the crude residue obtained in the DBU-catalyzed approach, showing the highly similar $R_f$ of the 3-nitrochromene **10** and the undesired byproduct **32**.


**Image 3.** TLC study of the crude residue obtained in the DBU-catalyzed approach.

**Appendix 4:** Figure 11**¡Error! No se encuentra el origen de la referencia.**, taken from the supporting information given by Mohanta and Bez, shows the $^{1}$H NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene. [7] The observed signals have the same chemical shifts than those obtained in Figure 3. Thus, both experimental approaches employed give the desired product. The difference between the spectra of this investigation project and the spectrum provided by Mohanta and Bez [7] is the interpretation of the signals between 7.50-7.30 ppm. In Figure 3 they are all considered as a single multiplet integrating for 7 H, whereas in Figure 11 that region is divided into two multiplets integrating for 2 H and 5 H. Nevertheless, in both cases, the total integration of that region is the same (7 H).

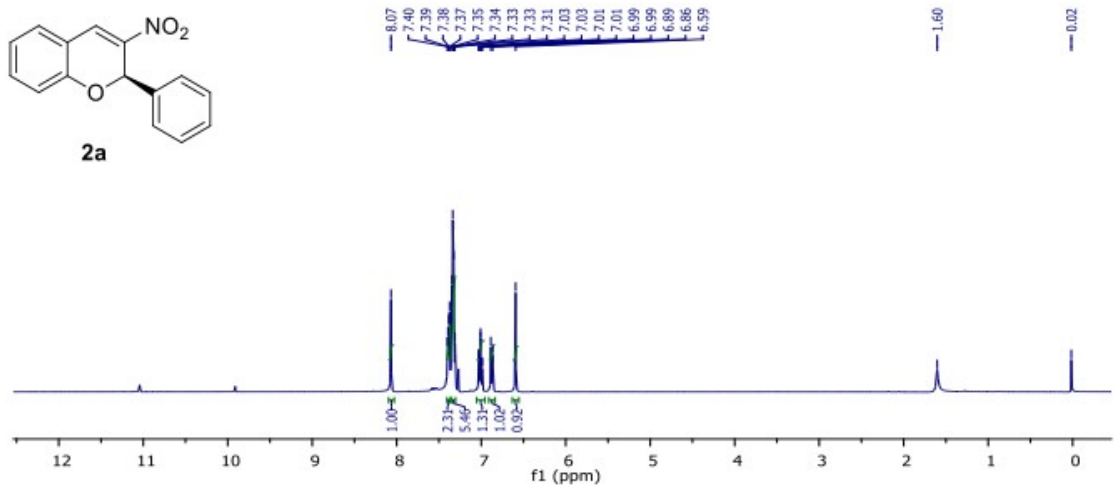


**Figure 11.** $^{1}$H NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene, obtained from Mohanta and Bez, done at 400 MHz and with $CDCl_3$ as solvent. [7]

**Appendix 5:** Figure 12**,** taken from the supporting information given by Mohanta and Bez, shows the $^{13}$C {$^{1}$H}-NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene. [7] The observed signals have the same chemical shifts than those obtained in Figure 4. Thus, it has once again been verified that the experimentally isolated product is the desired one.

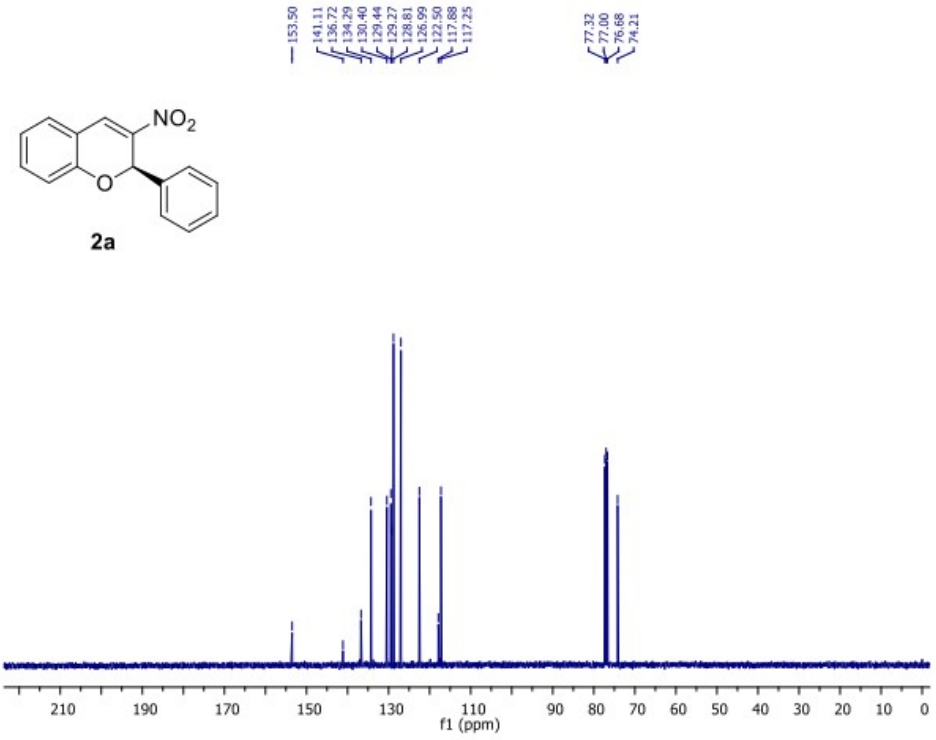


**Figure 12.** $^{13}C$ {$^{1}H$}-NMR spectrum of 3-nitro-2-phenyl-2*H*-chromene **10**, obtained from Mohanta and Bez, done at 100 MHz and with $CDCl_3$ as solvent. [7]

**Appendix 6:** Habib *et al.* describe in their research the $^{1}H$ NMR spectrum of the 1,2,3-triazole **24**: $^{1}H$ NMR ($CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 6.2 Hz, 2H), 7.37–7.29 (m, 4H), 7.05–7.02 (t, *J* = 7.0 Hz, 2H), 6.58 (s, 1H). [19] When comparing this spectrum with Figure 8, it can be concluded that the experimentally isolated product is the same compound. The signals have practically identical chemical shifts. The main difference between the spectrum obtained and that of the literature, is the interpretation of the signals between 7.50-7.30 ppm. In Figure 8 they are all considered as a single multiplet integrating for 6 H, whereas Habib *et al.* interpret them as one doublet integrating for 2 H and a multiplet integrating for 4 H. [19] Nevertheless, in both cases the total integration of that region is 6 H. The other difference between both spectra is that the doublet at 7.82 ppm of Figure 8 is described as a triplet by Habib *et al.* [19] The reason behind this discrepancy is that, in Figure 8, the small signal at 7.06 ppm is not considered as another peak but as a "shoulder" of the doublet.

**Appendix 7:** Habib *et al.* describe in their research the $^{13}C$ {$^{1}H$}-NMR spectrum of the 1,2,3-triazole **24**: $^{13}C$ NMR ($CDCl_3$) δ 153.5, 141.7, 138.9, 138.2, 130.5, 128.9, 128.8, 127.2, 1233, 122.4, 117.8, 116.0, 76.3. [19] The observed signals have very similar chemical shifts than those obtained in Figure 9. Thus, it has once again been verified that the isolated product is the desired one.