

PREPARATION OF *N*-HETEROCYC COMPOUNDS BY ENVIRONMENTALLY BENIGN CASCADE REACTIONS

Vanessza Judit Kolcsár,^{1,*} György Szöllösi²

¹*Department of Organic Chemistry, University of Szeged, Dóm tér 8, Szeged, 6720, Hungary.*

²*ELKH-SZTE Eötvös Loránd Research Network, Eötvös utca 6, Szeged, 6720, Hungary*

*Corresponding author: kolcsar.vanessza@chem.u-szeged.hu

Abstract

The *N*-heterocyclic compounds include various molecules with significant biological activity, such as the quinazolinone derivatives. The preparation, characterization and application of these molecules are in the focus of pharmaceutical chemistry. The mono- and disubstituted dihydroquinazolinone derivatives are potential anti-cancer and anti-inflammatory compounds, besides they can be used as other pharmaceutical and agrochemical ingredients [1]. Nowadays the demand for the protection of the environment is fortunately increasing, which places numerous expectation on the industries. In the fine chemical and pharmaceutical processes, it has become a basic requirement to take into account the 12 principles of green chemistry. Due to this, the catalytic and neat reactions along with the application of compound from sustainable sources, environmentally friendly solvents and alternative activation methods have a great importance. Among the alternative energy transmission methods, it is worth to highlight the implementation of the mechanochemistry, as the reactions carried out in ball mills, have many of the above-mentioned advantages.

In this present study, we examined the cascade reaction of anthranilamide and acetone, in which one ring-closing step occurs, and then we expanded the system to a bifunctional compound, ethyl levulinate, which is a renewable reaction partner, to achieve a second ring-closing step. We examined the possibilities of neat reactions, the quality of the applied catalyst, reaction temperature and time. After the successful optimization of the magnetically stirred neat reactions, we turned our focus to the mechanochemical activation of the reactions. It is possible to carry out several reactions neat in a ball mill, however generally better result can be achieved by adding a small amount of solvent to improve the mixing and the energy transition in the system [2]. Under the optimized conditions, the reactions were carried out with outstanding selectivity, and the final products were obtained in good yields.

The developed method provides essential experiences to synthesize optically pure *N*-heterocycles in a system that meets today's environmental expectations. The initial experiment of the reaction between anthranilamide and other bifunctional compounds was also carried out. It is our ongoing future goal to optimize the conventional, then the mechanochemical synthesis of optically pure condensed ring systems.

Introduction

Numerous methods are known for the synthesis of *N*-heterocycles, such as the aza-Wittig reaction of *o*-amino benzoic acid or anthranilamide and carbonyl compounds or esters [3]. The cascade reaction can be carried out in a Au(I)-catalysed one-pot system [4]. The reaction of anthranilamide with aldehydes and ketones starts with the formation of a Schiff-base, which cannot be isolated, then follows the ring-closing step. As long as the reactant of anthranilamide is bifunctional and bears the necessary structural characteristics, such as levulinic acid or its esters, the tandem reactions is continued with another ring closing [5]. To catalyse this latter step various homogenous and heterogeneous catalysts, for example Bronsted-acid are available. Although, these latter methods are successful, their sustainability should be increased. Various

alternative activation methods can be used, such as microwave and ultrasound assisted or mechanochemical reactions. Many advantages of the latter can be highlighted, starting from minimized solvent need to significantly shorter reaction times.

Due to the fast movement of the mixing mills, the collision and friction between the grinding media, the wall of the mixing jar and the components provide enough energy to activate various reactions. In most of the mechanochemical systems, the reactions are carried out neat. However, a small amount of liquid added to the system acts as an energy mediator, thus the term liquid assisted grinding (LAG) is used to describe these methods [2]. The application of mechanical energy transfer opens a path to carry our various catalytic reactions faster, than the conventional, thermally activated reactions [6,7].

Our aim was to develop an environmentally benign method for the synthesis of *N*-heterocycles, in the reaction of anthranilamide with acetone and bifunctional molecules, to achieve a second ring closing step in a one-pot cascade manner. As the reactant in the latter method ethyl levulinate was chosen, due to its sustainable properties, as the platform molecule, levulinic acid is obtained from renewable biomass sources, furthermore the esterification may be carried out in a neat and microwave activated organocatalytic system [8,9].

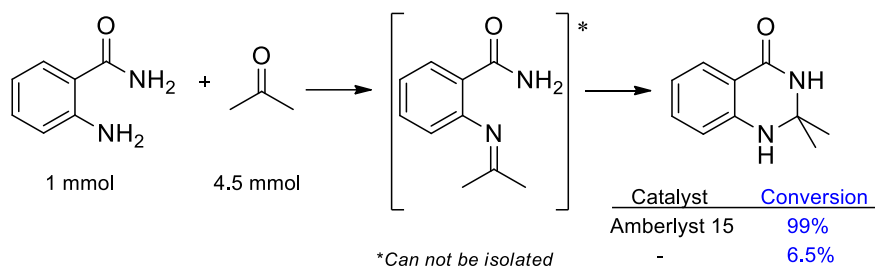
Experimental

The anthranilamide, acetone, ethyl levulinate and the catalyst (Amberlyst 15) were, obtained from commercial sources and were used as received. The conventional magnetically stirred cascade reactions were carried out in closed glass vials, which were immersed in heated oil bath if it was necessary. After the given reaction time the mixture was cooled to room temperature than 2 mL methanol (MeOH) was added to dissolve the product. The Amberlyst 15 beads were separated from the solution and were washed twice with 1 mL MeOH. In the mixing mill, during the reaction the Amberlyst 15 grinds to powder. To make the stirred and milled reactions comparable, the catalyst was pre-grinded at 30 Hz for 10 minutes, to obtain a homogenous powder. 2 mL MeOH was added to the reactions carried out with Amberlyst 15 powder, the catalyst was separated by centrifugation and was washed twice as before. The combined organic phases were analysed by GC-MSD and GC-FID.

The mechanochemical reactions were carried in 10 mL ZrO₂ grinding jars with milling balls made from the same material with the diameter of 5 mm. In a typical run all the compounds were measured into to the jars, then the necessary amount of balls was added into the system. The mixture then was agitated in a Retsch Mixing Mill MM 400 instrument at the desired frequency for the desired time. When the reaction was completed 2 mL MeOH was added, then the jars and balls were washed twice with 1 mL MeOH. The catalyst was separated by centrifugation, then was washed twice as in the case of the stirred reactions. The final product was purified by crystallisation from hexane and was analysed by NMR spectroscopy.

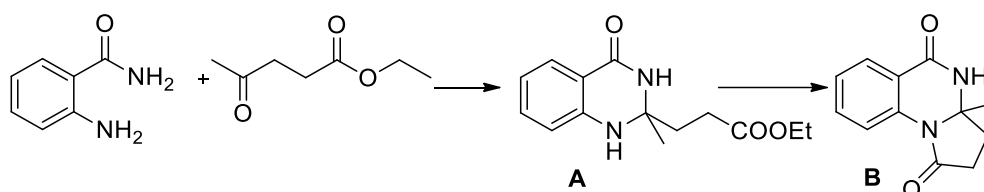
Results and discussion

Our first experiments were carried out in a conventional magnetically stirred system. The two-step reaction between anthranilamide and acetone was carried out neat, acetone acted as the solvent as it was introduced to the system in excess. The formation of the Schiff-base is fast, however, the ring-closing step demands a catalyst. The application of Amberlyst 15 was efficient to achieve closely full conversion, and only the expected compound with the condensed ring system was detected as the product.



Scheme 1. The reaction of anthranilamide and acetone with and without catalyst (24°C, 6h)

The one pot cascade reaction of anthranilamide and ethyl levulinate has similar first two steps as the Schiff-base is formed, followed by the first ring closing, although due to the bifunctional characteristics of the ketoester a second ring closing can occur. Similarly to the latter reaction, the reactant was added in excess (1.5 eq) to act as a solvent and to ensure the proper mixing of the system. The reaction was carried out at 60°C, and was stirred for 24 h.



Scheme 2. The reaction of anthranilamide and ethyl levulinate (60°C, 24h)

We examined the effect of the amount of catalyst first with the commercially available Amberlyst 15 beads. In this reaction the conversion was closely full, the amount of catalyst had no effect on this parameter, however the selectivities changed drastically. Figure 3 shows the selectivity of B as a function of the amount of catalyst, which gives a saturation curve. The powdered catalyst is more effective, probably due to the larger surface, better accessibility of the catalytic sites and more efficient distribution in the system. The main difference between the original and pre-grinded Amberlyst 15 is detectable when 50 mg of catalyst was applied. The conversion was the same, however the second ring-closing step was faster, when the powdered catalyst was applied. The magnetically stirred reaction was also carried out in the presence of an additional solvent, in our case, MeOH. To determine the amount of the added liquid, we choose to reduce the excess of the levulinate to 1.1 eq, and the missing volume (57 μL) was supplemented with MeOH. The effect of the solvent was examined in a 24 h reaction applying 50 mg powdered Amberlyst 15. As Figure 1. shows, a small amount of solvent improved the reaction, to reach almost full selectivity of the final, tricyclic product (**B**).

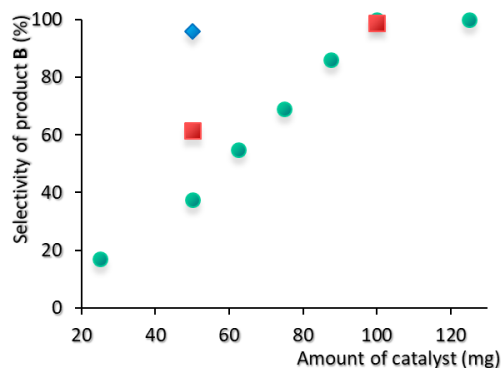


Figure 1. The selectivity of the reaction of anthranilamide and ethyl levulinate in batch reactor with the use of ●-commercially available and ■-pre-grinded Amberlyst 15, ◆-in the presence of MeOH

The next step was to examine the mechanochemical implementation of the cascade reaction between anthranilamide and ethyl levulinate. In a typical run 35 pieces of grinding balls with a diameter of 5 mm were applied, to provide enough collisions. As the Amberlyst 15 beads would have been grinded during the milling, in order to make the system reproducible, Amberlyst 15 powder was applied. The main advantage of the mechanochemical processes is that the reaction time can be significantly shortened compared to the thermally activated systems. We were able to shorten the 24 h reactions to only 3 h.

In the LAG method a small amount of liquid is necessary, which has an energy mediating role, besides it provides better mixing. The effect of the amount of MeOH is shown on Figure 2. The achieved result illustrates the energy mediating role of the liquid. The energy provided by the friction and collision of the grinding media is well distributed and transferred by the additional liquid. Furthermore, the added MeOH dissolves the compounds and helps to mix evenly with the catalyst on the surface of the balls. Although the reaction is not neat literally, LAG methods are still classified as environmentally friendly processes and MeOH is considered a green solvent.

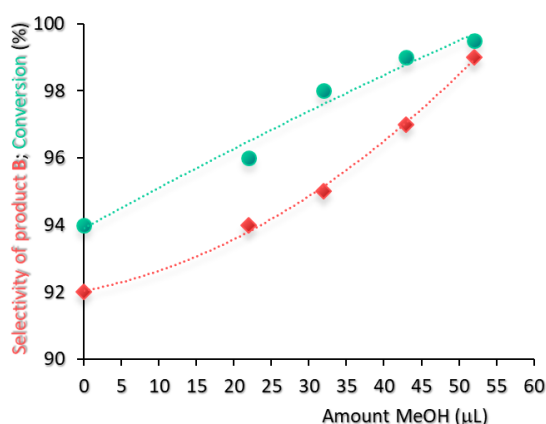


Figure 2. The effect of the amount of applied MeOH on the conversion and selectivity;
●-Conversion; ◆-Selectivity **B**

The milling time did not affect the conversion, due to the fast formation of the Schiff-base and the first ring-closing, however, the second ring-closing step is time consuming. The reaction was milled for 60, 90, 120 and 180 minutes, and the ratio of the product changed significantly. After 60 minutes only 41% **B** was detected, which increased to 71% and 75% after 90 and 120 minutes of grinding. To obtain the product after the second ring-closing in >99% at least 180 minutes were necessary at 30 Hz agitation frequency.

The amount of the transferred energy depends on the collision intensity, which is affected by the mass of the grinding balls [10] and the milling frequency. As the agitation was slower (20 Hz) the selectivity of **B** decreased from >99% to 18%, which shows the high activation energy of the second ring-closing step. The reaction was agitated at 30 Hz for 3 h, using different grinding balls. In the cases of the smaller milling media sizes (Ø3 and Ø5 mm) the number of balls were determined to apply similar total ball volumes and only 1 pc was added from the bigger (Ø12 and Ø15 mm) balls. Although the 125 pcs of the Ø3 mm beads provided enough collisions per unit of time, the kinetic energy of the light weighted balls, thus the intensity of the collisions was not enough to promote the second ring-closing. Figure 3. shows the importance of the intensity of collisions as less pcs of the Ø5 provided outstanding selectivity. In the case of the Ø12 and Ø15 mm balls, the mass, thus the energy of the grinding media was high, however due to the lack of collision points, the selectivity decreased drastically.

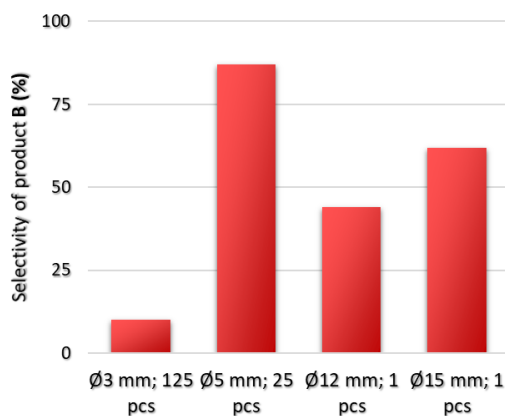


Figure 2. The effect of the applied balls on the selectivity

The reactions in both the magnetically stirred and the mechanochemical systems were carried out applying 1 mmol anthranilamide. The reactions were successful, and provided enough product to purify by crystallisation, thus, the method opens a new path for an environmentally benign synthesis of *N*-heterocyclic compounds.

Conclusion

In summary, we developed a sustainable system for the synthesis of *N*-heterocycles. The reactions were carried out neat in glass vials, and by a LAG method using a mixing mill. The mechanochemical implementation bears many advantages over the conventional magnetically stirred methods. The reaction time was shortened from 24 h to only 3 h, while the achieved conversion and selectivity remained the same. As the LAG method demands a small amount of additional liquid we aimed to apply a solvent which dissolves the starting compounds and the products, but most importantly complies with the principles of green chemistry. A small amount of methanol provided better mixing and had an energy mediating role, thus the mechanochemical reaction could be completed. The final product was separated from the heterogeneous catalyst by dissolving it in methanol, and then after evaporation, could be purified by crystallisation.

Our studies are the first steps to develop a sustainable method for even chiral *N*-heterocycles in the future. Furthermore, as a heterogeneous catalyst is applied, the possibility of reusing the catalyst may further improve the sustainability of the method.

Acknowledgements

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