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Research Article

Preparation of Al_2O_3-SO_3H and nano Al_2O_3-SO_3H as a heterogeneous catalyst for the one-pot tree component synthesis of Hexahydroquinazolinone

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ABSTRACT

An efficient and practical synthetic method has been developed for the preparation of hexahydroquinazolinone derivatives via a one-pot three-component catalytic reaction. The method involves the reaction of various aldehyde derivatives with urea and 1,3-cyclohexadiene in the presence of Al_2O_3-SO_3H and nano Al_2O_3-SO_3H, which serve as effective heterogeneous acid catalysts. These catalysts exhibited excellent performance under thermal conditions, affording the desired products in high purity and excellent yields within short reaction times. This process offers several notable advantages, including operational simplicity, minimal purification steps, and the use of inexpensive and readily available catalysts. Moreover, the products were easily purified by crystallization, and the catalysts proved to be reusable over multiple cycles without significant loss of catalytic activity or efficiency.

Keywords: *Heterogeneous* Acid *Catalysts, One-pot three-component Catalytic, Nano* Al_2O_3-SO_3H*, Hexahydroquinazolinone, Aldehyde.*

1. Introduction

Due to their advantages over conventional multistep synthesis, multicomponent reactions (MCRs) have emerged as a versatile approach in organic synthesis for building complex structures from simple building blocks [1]. They have obtained significant attention during the past few years; do not happen through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions [2-4]. MCRs are processes in which at least three different simple substrates react in one-pot to give the aim materials [5-7]. Although, MCRs have great contribution in conversant synthesis of important organic molecules from easy and readily existing starting materials, and have emerged as powerful tools for drug discovery [8, 9]. Simplicity, larger effectiveness, atom economy and generation of molecular complexity with diversity in one-pot transformations are some advantages of these reactions [10-12]. According to the principles of green chemistry, the elimination of harmful materials has become a huge challenge in both academic and industry projects [13, 14]. To deal with this target, decreasing the handling of toxic materials, using one-pot synthesis, and application of renewable, harmless, and reusable catalysts are the most important factors from the point of view of green chemistry [15-18]. Heterogeneous catalysts have recently attracted significant attention because of the increasing worldwide momentum toward the development of environmentally friendly reactions in terms of green chemistry [1, 19].

Nanoparticles (NPs) have drawn considerable interest in recent years because of their particular properties such as increased activity for use as catalysts, a large surface-to-volume ratio, and exclusive optical and electrical properties as compared to those of bulk materials [20, 21]. NPs referred to too much interest in different organic reactions provide their cost efficiency, experimental cleanness, and ease of handling [22-26]. Al_2O_3-SO_3H nanoparticles (NPS) have been intensively investigated because of their professional heterogeneous catalyst, low curie temperature, and high coercively [27, 28].

Following previous works in the preparation of heterocyclic compounds [29, 30], we report an efficient and novel method for the synthesis of hexahydroquinazolinone via one-pot MCRs of 1,3-cyclohexadione, aromatic aldehyde derivatives, and urea. In this protocol, the aforesaid desired compounds were prepared in excellent yields and with short reaction times by using Al_2O_3-SO_3H and nano Al_2O_3-SO_3H specific surface to volume, crystalline size as a robust as well as effective and easily recoverable catalyst. This reaction provided facile access to the target molecules in excellent yields, simplicity of the workup, low cost, and short reaction times.

Thus, a hybrid of these three motifs could potentially lead to a series of structurally and biologically interesting compounds (Fig 1).

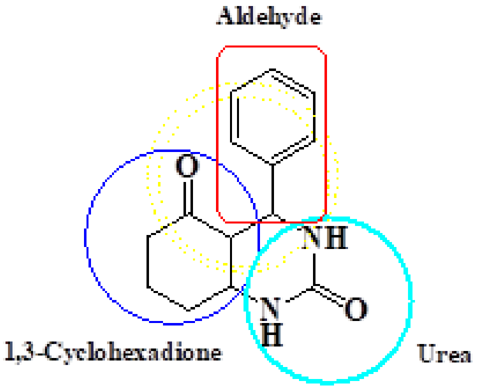


Fig. 1. Hybrid structure of some important heterocyclic compounds

2. Experimental

2.1. Chemicals and apparatus

All the materials were of commercial reagent grade. The chemical used in this work were obtained from Fluka and Merck and were used without purification. The FT-IR spectra were recorded on a Perkinelemer BX-II spectrophotometer. UV spectra (in EtOH) were recorded on a CINTRAL 101 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer in DMSO-*d6* solvents with tetramethylsilane as an internal reference. Mass spectra were obtained on a Platform II spectrometer from Micromass; EI mode at 70 eV. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel Polygram SILG/UV 254 plates (from Merck Company).

2.2. Preparation of Al_2O_3-SO_3H and nano Al_2O_3-SO_3H

In a typical procedure for the preparation of Al_2O_3-SO_3H, Al_2O_3 was dispersed in dry CH_2Cl_2 at room temperature under continuous stirring. After dispersing, 1 ml chlorosulfonic acid was added to the mixture of dispersion and stirred for 2h. Then the solution was filtered under reduced pressure and the obtained materials were carefully washed with dry CH_2Cl_2 and then dried at 120°C for 12 h. In this step, the modified Al_2O_3-SO_3H was obtained as a solid acid catalyst in the organic synthesis.

For the preparation of Al_2O_3-SO_3H, nano Al_2O_3 was dispersed in dry CH_2Cl_2 at room temperature under continuous stirring. After dispersing, 1 ml chlorosulfonic acid was added to the mixture of dispersion and stirred for 2h. Then the solution was filtered under reduced pressure and the obtained materials were carefully washed with dry CH_2Cl_2 and then dried at

120°C for 12 h. In this step, the modified Al_2O_3-SO_3H was obtained as a solid acid Nano catalyst in the organic synthesis.

2.3. General procedure for the one-pot preparation of Hexahydroquinazolinone

To prepare hexahydroquinazolinone, a mixture of aromatic aldehydes (10 mmol), 1,3-cyclohexadione (10 mmol), urea (20 mmol), and Al_2O_3-SO_3H (0.05 g) and acetonitrile (10 ml) were heated under reflux conditions for the appropriate time. The progress of the reaction was monitored by thin layer chromatography (TLC) (eluent: n-hexane/ethyl acetate (5:1).
After completion of the reaction the catalyst was filtered by simple filtration. The pure products were obtained by recrystallization from ethanol. All of the pure products were characterized by a comparison of their physical and spectral data with those of authentic samples.

The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature. The nanoparticles were easily separated from the reaction mixture with an external magnet and reutilized four times for the same reaction. The crude solids were filtered off and washed with water.

The pure products were obtained by recrystallization from methanol and were identified by physical and spectroscopic data (supplement).

3. Results and Discussion

3.1. Preparation of Al_2O_3-SO_3H and nano Al_2O_3-SO_3H

During the past few years, noteworthy interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically feasible.

Among different solid supports, alumina is an attractive support, inexpensive, existing, and nontoxic solid for the immobilization of organocatalysts as a result of its thermal and mechanical stability, as well as its chemical inertness.

Therefore, a heterogeneous catalyst has been prepared by Al_2O_3 and nano Al_2O_3 in the presence of chlorosulfonic acid as a sulfonated reagent (Figure 2).

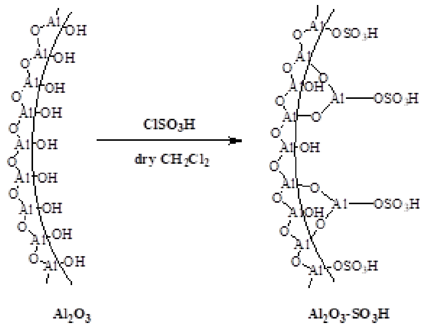


Fig. 2. Preparation of Al_2O_3-SO_3H

The functional groups attached to Al_2O_3 are quantitatively determined by back acid-base titration (-SO_3H) in Al_2O_3 0.2 mmol H^+ sites per 0.02g of Al_2O_3-SO_3H (values calculated by the weight of Al_2O_3-SO_3H at 25 ^oC. Also, the pH of resulted Al_2O_3-SO_3H (10% w/v) was determined using a pH meter. At first 1 g Al_2O_3-SO_3H was dispersed in 5ml H_2O by ultrasonic bath for 60 min, then calculated and roughly about 1.

3.2. General procedure for Biginelli type reaction catalyzed by Al_2O_3-SO_3H and nano Al_2O_3-SO_3H

The Al_2O_3-SO_3H and nano Al_2O_3-SO_3H were investigated in the synthesis of hexahydroquinazolinone. First, the reaction parameters such as solvent, temperature, and catalyst amount were optimized in the reaction of benzaldehyde, 1,3-cyclohexadione (1 mmol), and urea (1.5 mmol) in the presence of Al_2O_3-SO_3H nano Al_2O_3-SO_3H as a model reaction.

In our initial investigations, the model reaction was carried out using Al_2O_3-SO_3H as the catalyst in various solvents. The results are summarized in Table 1. No product was formed in the absence of the catalyst (Table 1 Entry 6). The reaction was first carried out in the presence of nano Al_2O_3-SO_3H as an inexpensive and available catalyst in different polar and non-polar solvents, under reflux conditions. The results are summarized in Table 1.

Upon screening various solvents to find out the best choice, it was found that the reaction with CH_3CN as solvent resulted in the most excellent yield and shortest reaction time. Therefore, CH_3CN was applied as the appropriate solvent for this reaction (Table 1, entry 5). It seems that the reaction proceeds in aprotic solvent better than in protic solvent. Good yields were obtained when the reactions were operated in an aprotic solvent such as acetonitrile (Table 1, entry 5). In water, the catalyst was not dispersed in the reaction medium and did not participate in the reaction (Table 1, entry 3). In another protic solvent such as EtOH, the progress of the reaction was better, giving the Biginelli type adduct in 50% and (Table 1, entry 4); these results show that protic solvents deactivate the sulfonic acid sites. The best results were achieved by carrying out the reaction under reflux conditions in the presence of the catalytic amount of nano Al_2O_3-SO_3H with CH_3CN.

The best condition was achieved using a mixture of the following materials benzaldehyde (10 mmol), 1,3-cyclohexadione (10 mmol), urea (15 mmol), and nano Al_2O_3-SO_3H (0.04 g) in acetonitrile (10 mL) under reflux condition. The progress of the reaction was followed by TLC using n-hexane/ethyl acetate (5:1) as eluents until the total disappearance of the 1,3-cyclohexadione. The results are reported in Table 1. All the products are characterized by m.p, UV-vis, FT-IR and ^{1}H NMR, ^{13}C NMR and MS spectroscopic (supplement).

Table .1. Synthesis of Hexahydroquinazolinone in the presence of Al_2O_3-SO_3H and nanoAl_2O_3-SO_3H under different reaction conditions [a].

Compound	Al_2O_3-SO_3H	Solvents	T (˚C)	Time (min)	Yield[b](%) Al_2O_3-SO_3H	Yield[b] (%) Nano Al_2O_3-SO_3H
1	0.04	no solvent	r.t	255	15	20
2	0.04	no solvent	100	180	20	30
3	0.04	H_2O	reflux	195	32	40
4	0.04	EtOH	reflux	180	45	60
5	0.04	CH_3CN	reflux	120	65	80
6	-	CH_3CN	reflux	120	0	0
7	0.03	CH_3CN	reflux	215	60	75
10	0.06	no solvent	4	240	5	20

[a] Reaction conditions: benzaldehyde (10 mmol), 1,3-cyclohexadione (10 mmol), urea (15 mmol), [b] isolated yield

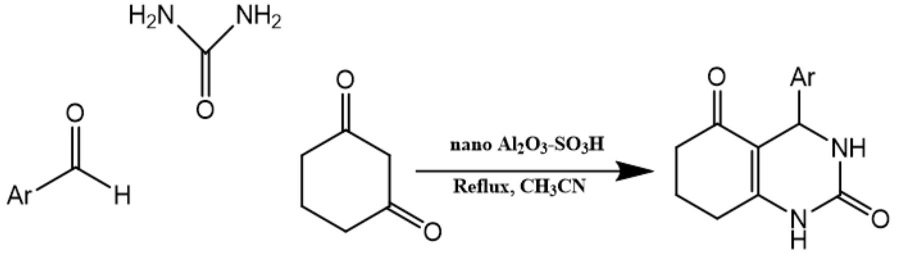
After optimization of the solvents and temperature, the condensation of benzaldehyde, 1,3-cyclohexadione, and urea in the presence of a catalytic amount of nano Al_2O_3-SO_3H with CH_3CN under reflux conditions was examined (Table 1, entries 1-10). It was found that the yield of the products was raised at higher temperatures in shorter reaction times in the presence of nano Al_2O_3-SO_3H versus Al_2O_3-SO_3H (Table 2, entry 5). It was concluded that the CH_3CN as solvent under reflux in the presence of 0.04 g of the catalyst is the optimized condition for this three-component reaction (Table 1, entry 5).

The catalyst plays an important role in the formation of 1,3-cyclohexadione derivatives. To compare the efficiency and effectiveness of the catalysts to improve the yield and to optimize the reaction conditions, the same reaction was carried out in refluxing water using different catalysts. The obtained results are outlined in Table 2. In the absence of the catalyst, the model reaction could be carried out but the product was obtained in very low yield during 48 h under reflux in CH_3CN and given by TLC analysis only a trace of the product. Therefore, our efforts focused on the search for a suitable catalyst.

The ascertain and limitation of the reaction, the reaction of 1,3-cyclohexadione with several aldehydes was carried out according to the general optimized experimental procedure. The corresponding products are summarized in Table 2. The yields of most products are higher than 80%. Thus, benzaldehydes bearing 4-substituents slightly afford better product yields. This slight difference is also seen in 2-substituted benzaldehydes. (Table 2). We proceeded to investigate the scope and limitations of our newly developed method using a variety of various aldehydes (Table 2). The results of these reactions exposed that aldehyde bearing an electron-donating (CH_3 or CH_3O) or electron-withdrawing (NO_2, Cl, Br) group were well tolerated under the optimized conditions, with the corresponding 4-substituted-hexahydroquinazolinone products 2a-2o being formed in good to high yields. There is more steric hindrance for the ortho-substituted aldehydes (-methyl, -methoxy, -Cl, -Br, -NO_2) decreasing both the reaction rate and the yield of the product.

Finally, Al_2O_3-SO_3H proved to be an efficient medium for the three-component reaction between 1,3-cyclohexadione, urea, and various aromatic aldehydes leading to the one-pot, synthesis of hexahydroquinazolinone derivatives. This method offered several advantages including; commercially available, and powerful nanocatalyst, the most environmentally accepted and abundant solvent. The operational simplicity of this method makes it more attractive for preparative applications. Excellent yields of the product, high purity, easy reaction conditions, high reaction rates, and easy work-up procedure. These results demonstrated that the catalyst was an efficient method for the one-pot synthesis of hexahydroquinazolinone as significant and profitable heterocycles.

Table. 2. Synthesis of hexahydroquinazolinone in the presence of nano Al_2O_3-SO_3H with CH_3CN under reflux conditions



1a

2a

Compound	Aldehyde	Time (min)	Yield[a] (%) Al_2O_3-SO_3H	Yield[a] (%) Nano Al_2O_3-SO_3H	m.p
2a	C_6H_5-	55	80	88	227 - 229
2b	4-CH_3-C_6H_4-	40	85	92	190 - 193
2c	3-CH_3-C_6H_4-	50	83	89	210 - 212
2d	2-CH_3-C_6H_4-	50	80	80	218 - 220
2e	4-CH_3O-C_6H_4-	60	88	91	198 - 202
2f	3-CH_3O-C_6H_4-	60	85	90	198 - 202
2g	2-CH_3O-C_6H_4-	60	75	80	208 - 209
2h	4-Cl-C_6H_4-	45	93	96	231 - 234
2i	3-Cl-C_6H_4-	40	86	90	218 - 219
2j	2-Cl-C_6H_4-	40	83	83	221 - 223
2k	4-Br-C_6H_4-	55	93	93	215 - 216
2l	3-Br-C_6H_4-	55	90	90	214 - 215
2m	2-Br-C_6H_4-	60	80	84	218 - 220
2n	4-NO_2-C_6H_4-	60	95	97	224 - 226
2o	3-NO_2-C_6H_4-	60	88	93	215 - 217
2p	2,6-dichlo-C_6H_4-	60	82	85	248 - 250

[a] isolated yield

Finally, as shown in Fig. 2, the reusability of the catalyst was investigated using 1,3-cyclohexadione, 4-nitro benzaldehyde, and urea, as model substrates. It is important to highlight that the catalyst could be recovered and washed with CH_2Cl_2. After being dried, it was subjected to another reaction. The procedure was repeated and the results indicated that the catalyst could be cycled four times without a significant loss of activity. The yields ranged from hexahydroquinazolinone 2n 97% to 79% (Fig 3).

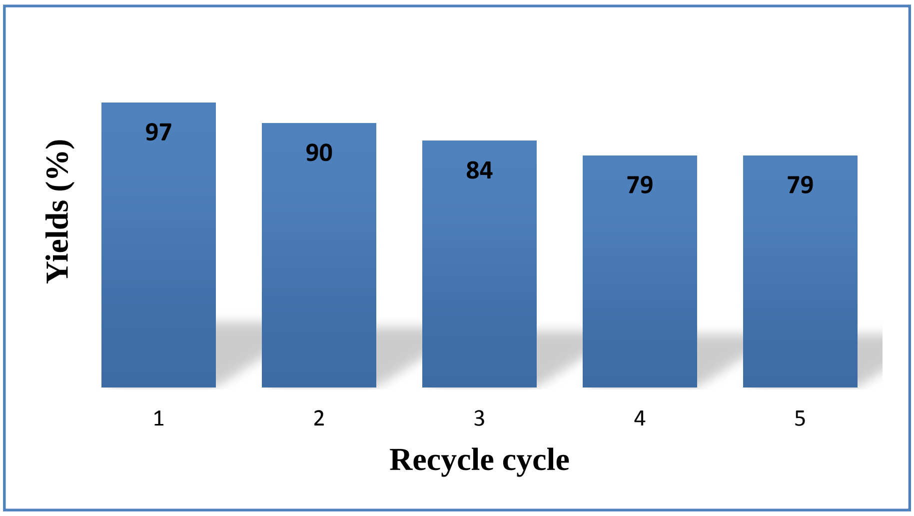


Fig. 3. Reusability of nanoAl_2O_3-SO_3H

3.4. Proposed reaction mechanism

Based on the results of the current study, we have proposed a mechanism for which is shown in Scheme 1. We propose a mechanism for the Al_2O_3-SO_3H catalyzed Biginelli type reaction. The aldehyde may react with urea to form an acyl imine intermediate, which is activated by H^+. Consequently, nucleophilic addition of the activated 1,3-cyclohexadione compound followed by cyclization and dehydration affords the hexahydroquinazolinone (Fig 4).

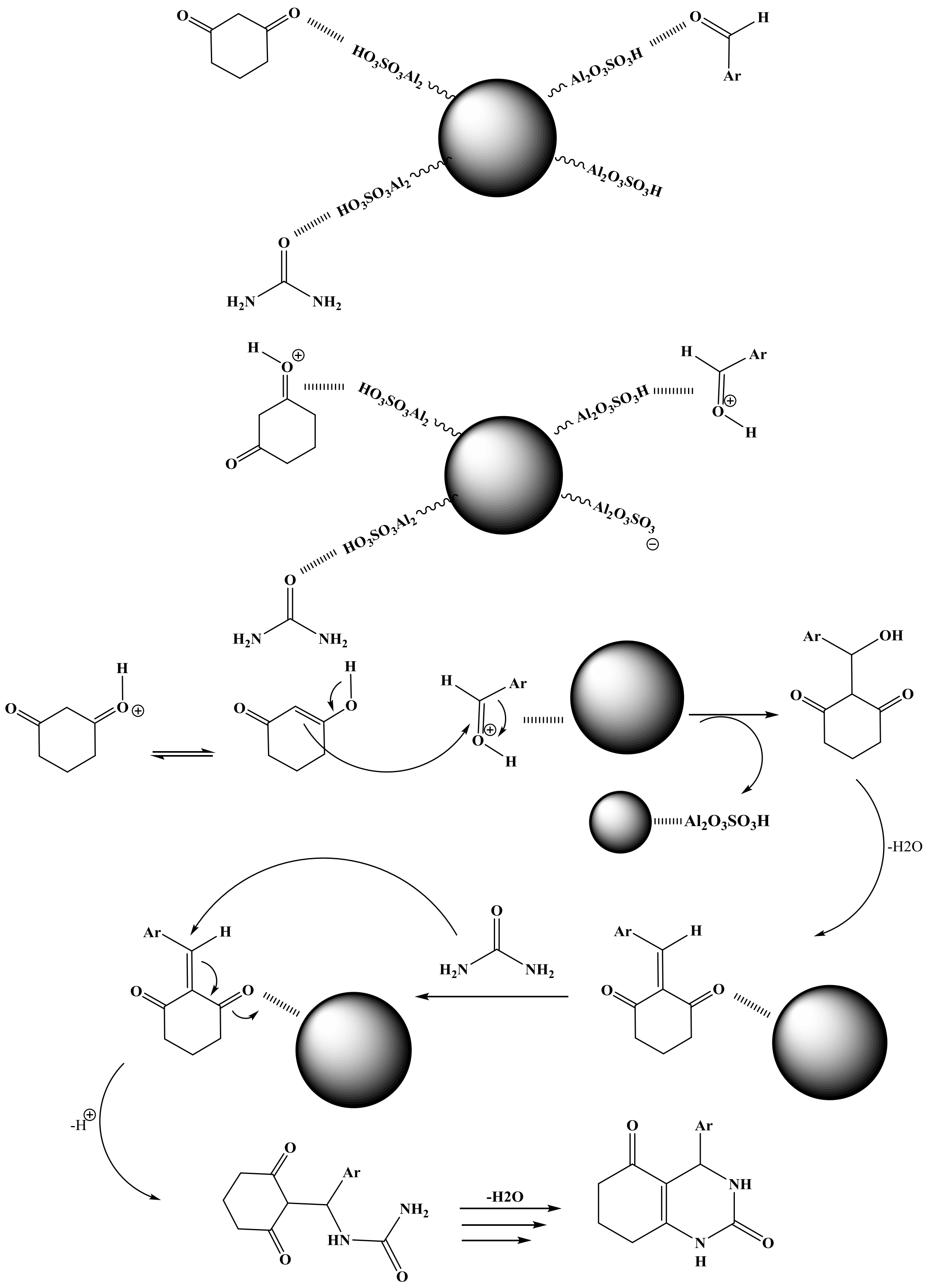


Fig. 4. Plausible mechanism for the preparation of Hexahydroquinazolinone

4. Conclusion

During the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically possible. Alumina is an attractive support for the immobilization of organocatalysts as a result of its thermal and mechanical stability, as well as its chemical inertness. These reasons prompted us to extend our work to the grafting of sulfonic acid onto alumina. In this method, we have described a highly efficient method for the one-pot three-component synthesis of hexahydroquinazolinone using nano Al_2O_3-SO_3H as an inexpensive, readily available, and reusable acid nano catalyst. These compounds were prepared through the treatment of 1,3-cyclohexadione, with various aromatic aldehydes and urea under reflux conditions. Furthermore, high yields of products, short reaction times, mild reaction conditions, and easy work-up are other noteworthy advantages that make this method a valid contribution to the existing methodologies.

References

[1] R. Ghahremanzadeh, Z. Rashid, A.-H. Zarnani, H. Naeimi, Journal of the Iranian Chemical Society, 11 (2014) 1407-1419 DOI: https://doi.org/10.1007/s13738-014-0422-x.

[2] L. Banfi, A. Basso, L. Giardini, R. Riva, V. Rocca, G. Guanti, *Tandem Ugi MCR/Mitsunobu cyclization as a short, protecting‐group‐free route to benzoxazinones with four diversity points*. 2011, Wiley Online Library.

[3] M. Climent, Chem. Rev, 111 (2011) 1072-1133.

[4] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, Chemistry–A European Journal, 6 (2000) 3321-3329 DOI: https://doi.org/10.1002/1521-3765(20000915)6:18<3321::AID-CHEM3321>3.0.CO;2-A.

[5] K. Kandhasamy, V. Gnanasambandam, Curr. Org. Chem, 13 (2009) 1820-1841.

[6] M. S. Singh, K. Raghuvanshi, Tetrahedron, 68 (2012) 8683-8697 DOI: https://doi.org/10.1016/j.tet.2012.06.099.

[7] L. F. Tietze, Chem. Rev., 96 (1996) 115-136 DOI: https://doi.org/10.1021/cr950027e.

[8] T. Zarganes-Tzitzikas, A. L. Chandgude, A. Dömling, The Chemical Record, 15 (2015) 981-996 DOI: https://doi.org/10.1002/tcr.201500201.

[9] H. B. d. Lima, G. M. d. Neves, I. L. Gonçalves, A. A. Merlo, V. L. Eifler-Lima, J. Braz. Chem. Soc., 35 (2024) e-20240075.

[10] K. Murai, R. Nakatani, Y. Kita, H. Fujioka, Tetrahedron, 64 (2008) 11034-11040 DOI: https://doi.org/10.1016/j.tet.2008.09.076.

[11] M. Lebl, J. Comb. Chem., 1 (1999) 3-24.

[12] M. Ghandi, T. Momeni, M. T. Nazeri, N. Zarezadeh, M. Kubicki, Tetrahedron Lett., 54 (2013) 2983-2985 DOI: https://doi.org/10.1016/j.tetlet.2013.03.131.

[13] O. V. Kharissova, B. I. Kharisov, C. M. Oliva González, Y. P. Méndez, I. López, R. Soc. Open Sci., 6 (2019) 191378 DOI: https://doi.org/10.1098/rsos.191378.

[14] R. A. Sheldon, M. L. Bode, S. G. Akakios, Curr. Opin. Green Sustainable Chem., 33 (2022) 100569 DOI: https://doi.org/10.1016/j.cogsc.2021.100569.

[15] S. Ghotekar, T. Pagar, S. Pansambal, R. Oza, Advanced Journal of Chemistry-Section B, 2 (2020) 128-143 DOI: https://doi.org/10.33945/SAMI/AJCB.2020.3.5.

[16] O. El-Shahaby, F. Reicha, M. N. Aboushadi, M. El-Zayat, Prog. Chem. Biochem. Res., 3 (2020) 105-113 DOI: https://doi.org/10.33945/SAMI/PCBR.2020.2.3.

[17] A. Fallah, M. Tajbakhsh, H. Vahedi, A. Bekhradnia, Res. Chem. Intermed., 43 (2017) 29-43 DOI: https://doi.org/10.1007/s11164-016-2603-y.

[18] Z. Kheilkordi, G. M. Ziarani, A. Badiei, Polyhedron, 178 (2020) 114343 DOI: https://doi.org/10.1016/j.poly.2019.114343.

[19] R. Sharma, D. Rawat, G. Gaba, Catal. Commun., 19 (2012) 31-36 DOI] R. K. Sharma, D. Rawat and G. Gaba, Catal. Commun., 2012, 19, 31-36.

[20] Y. Zhao, J.-M. Hong, J.-J. Zhu, J. Cryst. Growth, 270 (2004) 438-445 DOI: https://doi.org/10.1016/j.jcrysgro.2004.06.036.

[21] F. A. La Porta, M. M. Ferrer, Y. V. De Santana, C. W. Raubach, V. M. Longo, J. R. Sambrano, E. Longo, J. Andrés, M. S. Li, J. A. Varela, J. Alloys Compd., 556 (2013) 153-159 DOI: https://doi.org/10.1016/j.jallcom.2012.12.081.

[22] J. Nam, N. Won, J. Bang, H. Jin, J. Park, S. Jung, S. Jung, Y. Park, S. Kim, Adv. Drug Delivery Rev., 65 (2013) 622-648 DOI: https://doi.org/10.1016/j.addr.2012.08.015.

[23] Y. Zhu, Q. Ruan, F. Xu, Nano Research, 2 (2009) 688-694 DOI: https://doi.org/10.1007/s12274-009-9072-1.

[24] M. Moritz, M. Geszke-Moritz, Chem. Eng. J., 228 (2013) 596-613 DOI: https://doi.org/10.1016/j.cej.2013.05.046.

[25] B. Hemmateenejad, S. Yousefinejad, J. Mol. Struct., 1037 (2013) 317-322 DOI: https://doi.org/10.1016/j.molstruc.2013.01.009.

[26] B. Sotillo, P. Fernández, J. Piqueras, J. Alloys Compd., 563 (2013) 113-118 DOI: https://doi.org/10.1016/j.jallcom.2013.02.109.

[27] A. Farhadi, M. A. Takassi, M. Enjilzadeh, F. Davod, J. Appl. Chem., 12 (2018) 48-57.

[28] N. Seif, A. Farhadi, R. Badri, A. R. Kiasat, J. Appl. Chem., 15 (2021) 8-18.

[29] M. Mehrabi, A. Farhadi, A. Kiassat, J. Org. Chem., 7 (2017) 240-253.

[30] M. Mehrabi, A. Farhadi, A. Kiassat, J. Appl. Chem., 15 (2021) 21-43.