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# Synthesis of 2,3-Disubstituted-4(3*H*)-quinazolinones Using HY-Zeolite as Reusable Catalyst Under Microwave Irradiation

NASER MONTAZERI*, KHALIL POURSHAMSIAN, ARSALAN FOMANI and SEYD JAFAR KALANTARIAN

Department of Chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

*Corresponding author: Fax: +98 192 4274409; Tel:+98 192 4274415; E-mail: montazer50@toniau.ac.ir

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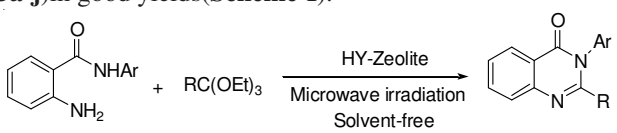
A new heterogeneous catalytic method to synthesize to various 4(3*H*)-quinazolinone derevatives, using an inexpensive and eco-friendly attractive solid catalyst, zeolite, under solvent-free and microwave irradiation conditions is described. The catalyst activity results suggest that the methodology adopted offers several advantages such as mild reaction conditions, low loading of catalyst, good yields, short reaction time and operational simplicity.

**Key Words: 4(3*H*)-Quinazolinones, HY-Zeolite, Solvent-free, Microwave irradiation.**

## INTRODUCTION

4(3*H*)-Quinazolinone derivatives have received considerable interest from the pharmaceutical industries due to their wide range of interesting biological and therapeutic properties, such as antimalarial, antitumor, anticonvulsant, antiinflammatory, fungicidal, antimicrobial, antagonist and catalytic activities[1-10]. In addition, 4(3*H*)-quinazolinones are present in several bioactive natural products[11,12]. Also, quinazolinone moity is a building block for approximately 150 naturally occurring alkaloids, including glycosminine, deoxyvasicinone, like methaqualone and piriqualon[13-16]. Because of these widespread activities, their synthesis was continually the subject of much research[17] and still pursued due to new emerging methods, such as microwave heating[18]. Performing reactions under microwave irradiation frequently gives rise to some rate enhancement and improvement of yields. Microwave irradiation conditions are best suited to the so-called solvent-free reactions. These reactions are eco-friendly and, in view of green chemistry,s desire to avoid solvent hazards, are in demand. There are several methods for the synthesis of 4(3*H*)-quinazolinones using DDQ/DMF[19], $Ga(OTf)_3$[20], $Yb(OTf)_3$[21], $Sc(OTf)_3$[22], $CuCl_2$ in ethanol[23], $I_2/KI$[24], *p*-toluenesulfunic acid/DDQ[25], $Al(NO_3)_3.9H_2O$[26] and $KMnO_4$[27], as catalyst. Other method such as cyclocondensation of 2-aminobenzamides with substituted benzoyl chlorides is also reported for synthesis of these compounds[28]. However, most of these procedures have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions and difficult work-up. Therefore, the development of simple, efficient, clean, high-yielding and environmentally friendly approaches using new catalyst for the synthesis of these compounds is an important task for organic chemists. Application of solid acids in organic transformations is important because they have many advantages including ease of products separation, recycling of the catalyst and environmental acceptability as compared to liquid acid catalysts[29]. Zeolites and clays are strong bronsted acids and have been used as catalysts for various organic reactions[30-32]. They are not only useful in terms of yield and selectivity but also concerning the work-up and effluent pollution. In spite of these advantages however their application in heterocyclization reactions has not fully been exploded. To our knowledge, there has been no report on the use of HY-zeolite as a solid catalyst under microwave irradiation and solvent-free reaction conditions in the synthesis of 4(3*H*)-quinazolinones. As a finding of our ongoing research projects on the synthesis of heterocyclic compounds[33-35] and in continuation of our previous works on the applications of solid acid catalysts in organic reactions[36-40], we now report that microwave-assisted cyclocondensation of 2-aminobenzamides (**1**) with triethylorthoesters (**2**) using HY-zeolite as solid acid catalyst quickly provides the 2,3-disubstituted 4(3*H*)-quinazolinones (**3a-j**)in good yields(**Scheme-I**).




**1** **2** **3a-j**

**Scheme-I:** Synthesis of 4(3*H*)-quinazolinones catalyzed by HY-zeolite

TABLE-1
REACTION OF DIFFERENT 2-AMINOBENZAMIDES WITH TRIETHYLORTHOESTERS EMPLOYING PFPAT CATALYST[a]

| Entry | R | Ar | Product | Yield[b] | m.p. (°C) | Lit. m.p. (°C)[ref] |
|---|---|---|---|---|---|---|
| 1 | H | Ph | **3a** | 83 | 137-138 | 139-141[26] |
| 2 | Me | ph | **3b** | 79 | 148-149 | 147-148[24] |
| 3 | ph | ph | **3c** | 80 | 159-160 | 158[23] |
| 4 | Et | 4-$MeC_6H_4$ | **3d** | 81 | 162-163 | 162-163[10] |
| 5 | Me | 4-$ClC_6H_4$ | **3e** | 78 | 158-159 | 157-158[27] |
| 6 | ph | 4-$ClC_6H_4$ | **3f** | 82 | 190-191 | 189-190[28] |
| 7 | H | 4-$MeC_6H_4$ | **3g** | 85 | 143-144 | 145-148[26] |
| 8 | Me | 4-$MeC_6H_4$ | **3h** | 77 | 150-152 | 151-152[39] |
| 9 | Ph | 4-$MeC_6H_4$ | **3i** | 84 | 180-182 | 180-181[39] |
| 10 | Pr | 4-$MeC_6H_4$ | **3j** | 86 | 143-145 | 145[10] |

[a]1 mmol 2-aminobenzamide, 2 mmol triethylorthoester and 0.1 g HY-zeolite under solvent-free and microwave irradiation conditions. [b]The yields were calculated based on 2-aminobenzamide and refer to the pure isolated product

## EXPERIMENTAL

All chemicals were available commercially and used without additional purification. In all cases the products were identified by their spectroscopic properties and comparison with authentic samples[10,23-28]. All reactions were carried out in a CEM MARS 5™ microwave oven. 2-Aminobenzamides (**1**) were prepared according to a reported method[41]. Melting points were recorded on an electrothermal type 9100 melting points apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. $^1$H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometers.

**General procedure for synthesis of 2,3-disubstituted 4(3*H*)-quinazolinones 3a-j catalyzed by HY-zeolite:** A mixture of 2-aminobenzamide **1** (1 mmol), triethylorthoester **2** (1 mmol in each case) and HY-zeolite (0.1 g) was placed in a 50 mL beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for 3 min with power of 210 W. After cooling to room temperature, the beaker was irradiated again for 4 min at 385 W. The progress of reaction was monitored by TLC. After completion of the reaction, hot residue was dissolved in ethanol. The solid catalyst was filtered off and the fairly pure crystals of products that separated on cooling from the filtrate solution were further recrystallized in ethanol.

**Recycling and reusing of catalyst:** After the completion of the reaction, hot ethanol was added. The catalyst was recovered by filtration, washed with *n*-hexane, dried at 120 ºC for 1 h and reused in another reaction. The catalyst could be reused at least three times with only slight reduction in the catalytic activity of the catalyst.

## RESULTS AND DISCUSSION

The synthesis of fine chemical under environmentally friendly conditions represents a challenging goal in the field of synthetic organic chemistry[42-44]. In the last two decade this approach has had a termendouse development, mainly due to the use of solid acids such as clays and zeolites[45-47]. Also the development of heterogeneous catalysts for organic synthesis has become a major area of research. The potential advantages of these materials over homogeneous systems could lead to novel, environmentally benign chemical procedures for academia and industry[48-50]. The one-pot synthesis of 4(3*H*)-quinazolinones (**3a-j**) was achieved by cyclocondensation of 2-aminobenzamides (**1**) and triethylorthoesters (**2**) in presence of HY-zeolites as a low cost, nontoxic and inexpensive catalyst under microwave irradiation and solvent-free reaction conditions (**Scheme-I**). To find the optimum quantity of HY-zeolite, the synthesis of **3a** was used as a model reaction. Therefore, the reaction of 2-aminobenzamide (**1**) (Ar = Ph), (1 mmol) and triethylorthoformate (**2**) (R = H), (2 mmol) was carried out under microwave irradiation and solvent- free conditions, using different quantities of HY-zeolite. No product could be detected in the absence of this catalyst, while good results were obtained in the presence of HY-zeolite. The optimal amount of the catalyst was 0.1 g, the higher amount of the catalyst did not increase the yield noticeably. Based on the above result, this process was then extended to variety of 2-aminobenzamide derivatives and triethylorthoesters at the optimized system. The type of 2-aminobenzamides and triethylorthoesters no significant effect on the reaction. In all cases, reactions reacted successfully and gave the expected products in good yields in short reaction times. The results are summarized in Table-1.

Reusability of the catalyst was also investigated. For this purpose, the reaction of 2-aminobenzamide (**1**) (Ar = Ph) with triethylorthoformate (**2**) (R = H) was again studied under the optimized conditions. After completion of the reaction, ethanol was added. The catalyst was filtered under hot condition, dried and reused for the same reaction process. The catalyst could be reused at least three times with only slight reduction in the catalytic activity of catalyst.

### Conclusion

In conclusion, we have successfully developed a simple, mild and efficient methodology for the preparation of a wide variety of 4(3*H*)-quinazolinones through reaction of 2-aminobenzamides and triethylorthoesters employing HY-zeolite as the recyclable solid acid catalyst under solvent-free and microwave irradiation conditions. Other advantages of this protocol are good yields, short reaction time, easy work-up and omitting any volatile and hazardous organic solvents.

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