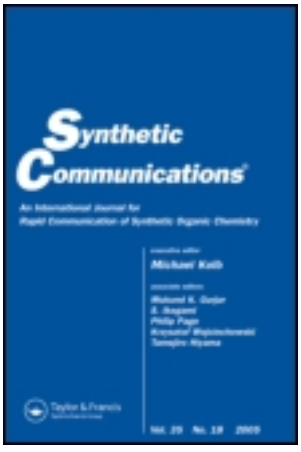

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One-Pot, Three-Component Synthesis of 2,3-Dihydro-4(1H)-quinazolinones by Montmorillonite K-10 as an Efficient and Reusable Catalyst

Peyman Salehi [a] , Minoo Dabiri [b] , Mostafa Baghbanzadeh [b] & Mahboobeh Bahramnejad [b]

[a] Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Evin, Tehran, Iran

[b] Department of Chemistry, Faculty of Science, Shahid Beheshti University, Evin, Tehran, Iran

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Peyman Salehi
Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Evin, Tehran, Iran

Minoo Dabiri, Mostafa Baghbanzadeh, and Mahboobeh Bahramnejad
Department of Chemistry, Faculty of Science, Shahid Beheshti University, Evin, Tehran, Iran

Abstract: A wide range of mono- and disubstituted dihydroquinazolinones were synthesised via condensation of isatoic anhydride, primary amines, or ammonium salts with aromatic aldehydes in the presence of montmorillonite K-10. The catalyst is reusable and could be recycled for several runs without any decrease in its efficiency.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-ones, heterogeneous catalysis, montmorillonite K-10

INTRODUCTION

Compounds with biological activity are often derived from heterocyclic structures. Indeed, one of the richest sources of diversity for medicinal chemists is small heterocyclic rings, which, in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities.

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Address correspondence to Peyman Salehi, Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Evin, P.O. Box 19835-389, Tehran, Iran. E-mail: p-salehi@cc.sbu.ac.ir

2,3-Dihydroquinazolinones are one such class of heterocycles that attracted much attention because they have been reported to possess a wide range of pharmaceutical activities including antifertility, antibacterial, antitumor, antifungal, and mono amine oxidase inhibitory activity.[1–4]

There are several methods for the preparation of this class of compounds. Among them, the most direct procedure includes condensation of aryl, alkyl, and heteroaryl aldehydes with anthranilamide in the presence of *p*-toluenesulfonic acid as a catalyst.[5,6] Reductive cyclization of *o*-nitrobenzamide or *o*-azidobenzamide with metallic samarium and catalytic amounts of iodine was also used for the synthesis of 2,3-dihydroquinazolinones.[7] On the basis of this procedure, Shi et al. has reported a new method for the synthesis of these compounds.[8]

The use of heterogeneous and reusable catalysts represents one of the most powerful and green procedures in chemical technology. Environmentally benign solid catalysts such as clays and zeolites instead of mineral acids are employed for acid-catalyzed organic reactions.[9]

Montmorillonite K-10 is the most important smectite used in catalytic reactions. High cation-exchange capacity (CEC) and good swelling properties allow the existence of a wide variety of catalytically active forms of montmorillonite (containing acidic cations, metal complexes, photocatalysts, active cations, etc.).[10]

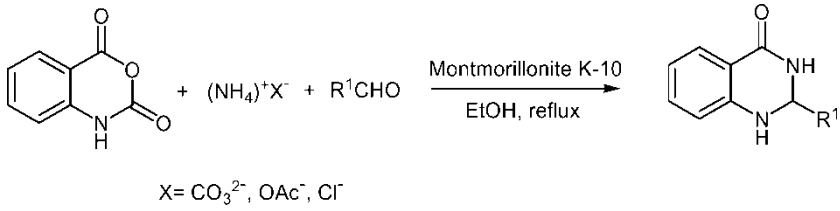
RESULTS AND DISCUSSION

In continuation of our investigations on the use of heterogeneous catalysts for the fine chemical preparation,[11–15] here one-pot condensation of primary amines or ammonium salts and aromatic aldehydes with isatoic anhydride in the presence of montmorillonite K-10 is reported. The reactions were carried out in refluxing ethanol, and the corresponding mono- and disubstituted derivatives of 2,3-dihydro-4(1*H*)-quinazolinone were obtained in high yields.

The use of ammonium salts as a productive source of ammonia in synthetic reactions has been well known for a long time.[16–19] Similarly, monosubstituted 2,3-dihydro-4(*1H*)-quinazolinones were synthesized efficiently by the condensation of isatoic anhydride and aromatic aldehydes in the presence of ammonium salts and montmorillonite K-10 under heterogeneous conditions (Scheme 1). The results are summarized in Table 1.

To compare the efficiency of ammonium salts, the reactions were carried out with different counter ions such as carbonate, acetate, and chloride under the same conditions. In all cases, monosubstituted 2,3-dihydro-4(1*H*)-quinazolinones were produced in good yields; however, the best yields were obtained with ammonium carbonate (Table 1).

Moreover, treatment of isatoic anhydride and aryl aldehydes with primary aliphatic and aromatic amines in the presence of montmorillonite K-10 in



Scheme 1.

refluxing ethanol afforded disubstituted derivatives of 2,3-dihydro-4(1*H*)-quinazolinone in good yields (Scheme 2). The results are represented in Table 2.

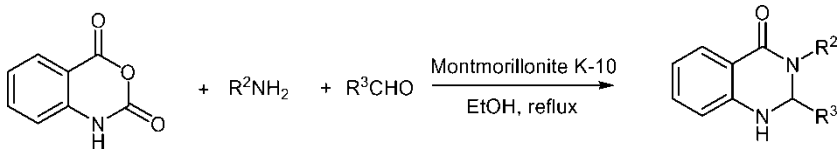
Aliphatic and aromatic amines afforded the products in good yields. However, aliphatic amines gave the products in shorter periods in comparison with aromatic amines, probably because of their higher nucleophilicity.

To investigate the possibility of recycling the catalyst, an investigation was made on the reaction of isatoic anhydride, ethylamine, and

Table 1. Synthesis of monosubstituted 2,3-dihydroquinazolin-4(*1H*)-ones with different ammonium salts in the presence of montmorillonite K-10 in ethanol

Entry	R^1	X	Time (h)	Yield[a] (%)	Mp (°C)
1	Ph	CO_3^{2-}	4	85	218–220[9]
2	4-ClC_6H_4	CO_3^{2-}	5	95	198–200[9]
3	4-$CH_3OC_6H_4$	CO_3^{2-}	7	85	178–180[9]
4	2-$CH_3OC_6H_4$	CO_3^{2-}	4	77	165–167[3]
5	4-$CH_3C_6H_4$	CO_3^{2-}	5	75	233–234[19]
6	3,4-$(CH_3O)_2C_6H_3$	CO_3^{2-}	5	80	210–213[3]
7	2-Furyl	CO_3^{2-}	4	80	165–167[19]
8	Ph	CH_3COO^-	4	72	218–220[9]
9	4-ClC_6H_4	CH_3COO^-	5	80	198–200[9]
10	4-$CH_3OC_6H_4$	CH_3COO^-	7	73	178–180[9]
11	2-$CH_3OC_6H_4$	CH_3COO^-	4	72	165–167[3]
12	4-$CH_3C_6H_4$	CH_3COO^-	5	73	233–234[19]
13	3,4-$(CH_3O)_2C_6H_3$	CH_3COO^-	5	75	210–213[3]
14	2-Furyl	CH_3COO^-	4	77	165–167[19]
15	Ph	Cl^-	4	70	218–220[9]
16	4-ClC_6H_4	Cl^-	5	77	198–200[9]
17	4-$CH_3OC_6H_4$	Cl^-	7	73	178–180[9]
18	2-$CH_3OC_6H_4$	Cl^-	4	70	165–167[3]
19	4-$CH_3C_6H_4$	Cl^-	5	70	233–234[19]
20	3,4-$(CH_3O)_2C_6H_3$	Cl^-	5	73	210–213[3]
21	2-Furyl	Cl^-	4	75	165–167[19]

[a]Isolated yield.



Scheme 2.

4-nitrobenzaldehyde. No decrease in catalytic activity of montmorillonite K-10 was observed after five runs (Table 2, entry 6).

It is worth noting that the purification procedure was extremely simple, including removal of the catalyst by filtration followed by a recrystallization step.

In conclusion, we report a simple and eco-friendly procedure for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones. Ease of workup, the use of easily accessible and inexpensive starting materials, and utility for the synthesis of a wide range of derivatives are the highlights of this new process. The catalyst is reusable and can be recycled for several runs. The procedure enjoys the chemical and economical advantages of multi-component reactions.

EXPERIMENTAL

All of the products are known compounds and were identified by comparison of their physical and spectroscopic data (IR, ^{1}H NMR) with those of authentic

Table 2. Synthesis of disubstituted 2,3-dihydroquinazolin-4(*1H*)-ones in the presence of montmorillonite K-10 in ethanol

Entry	R^2	R^3	Time (h)	Yield[a] (%)	Mp (°C)
1	Me	Ph	3	82	165[20]
2	Me	4-ClC_6H_4	3.5	83	190[20]
3	Me	4-$CH_3OC_6H_4$	3	80	146[20]
4	Et	Ph	3.5	85	134–137[20]
5	Et	4-ClC_6H_4	3.5	84	132–135[20]
6	Et	4-$O_2NC_6H_4$	3	90,91,89,87,92[b]	159–162[20]
7	Et	3-$O_2NC_6H_4$	3	92	176–178[20]
8	Et	4-$CH_3OC_6H_4$	4	84	124–126[20]
9	Ph	Ph	6.5	80	205–208[21]
10	Ph	4-$O_2NC_6H_4$	7	78	195–197[21]
11	Ph	4-ClC_6H_4	6	80	214–217[21]
12	Ph	3-$O_2NC_6H_4$	5.5	83	186–188[21]
13	4-ClC_6H_4	Ph	7	73	214–217[21]

[a]Isolated yield.
[b]The reaction was run for five cycles.

samples. Yields refer to isolated products. Melting points were obtained in open capillaries on an Electrothermal 9100 melting-point apparatus and were not corrected.

General Procedure for the Synthesis of Monosubstituted Derivatives of 2,3-Dihydro-4(1*H*)-quinazolinone

Montmorillonite K-10 (0.3 g) was added to a solution of isatoic anhydride (1 mmol), ammonium salt (ammonium carbonate, 0.6 mmol; ammonium acetate, 1.2 mmol; ammonium chloride, 1.2 mmol), and aromatic aldehyde (1 mmol) in ethanol (5 ml). The mixture was stirred for the appropriate period of time (Table 1). The solid catalyst was separated by filtration, and the residue was concentrated to afford the crude product. Final purification was achieved by recrystallization from ethanol.

General Procedure for the Synthesis of Disubstituted Derivatives of 2,3-Dihydro-4(1*H*)-quinazolinone

Isatoic anhydride (1 mmol) and primary amine (1.2 mmol) were dissolved in ethanol (5 ml). Then aromatic aldehyde (1 mmol) and montmorillonite K-10 (0.3 g) were added subsequently to the solution. The resulting mixture was stirred magnetically under reflux conditions. Upon completion of the reaction, confirmed by TLC (eluent: *n*-hexane/ethyl acetate, 2/1), the mixture was filtered and the residue was concentrated. The crude products were recrystallized from ethanol.

ACKNOWLEDGMENT

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