Iranian Journal of Organic Chemistry Vol. 4, No. 2 (2012) 827-830

Malonic acid as a catalyst for efficient and simple synthesis of 2,3-dihydroquinazolin-4(1H)-ones in green solvent

Somayeh Esfandiari, Malek Taher Maghsoodlou*, Sayyed Mostafa Habibi-Khorassani, Shiva kiaee and Jasem Aboonajmi

Department of Chemistry, Faculty of Science, University of Sistan and Baluchestan, P. O. Box: 98135-674, Zahedan, Iran

Received: April 2012; Revised: April 2012; Accepted: April 2012

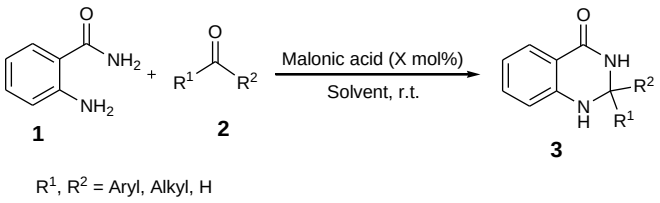
Abstract: A efficient method has been developed for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)- ones using 10 mol% malonic acid as a catalyst. It was prepared via condensation of 2-aminobenzamide with aldehydes or ketones in water and ethanol (1:1) at room temperature. The reaction proceeded in a short period of time with excellent yields.

Keywords: Malonic acid, 2-aminobenzamide, aldehyde, ketone, 2,3-Dihydroquinazolin-4(1H)-ones.

Introduction

2,3-Dihydroquinazolin-4(1H)-ones, an important class of heterocyclic compounds influence numerous cellular processes. This is exemplified by their broad range of pharmacological properties, for example, anticancer, antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic and diuretic activities [1-11]. Several methods for the synthesis of these compounds have been reported. Among them, the general method includes condensation of aldehydes or ketones with 2-aminobenzamide in the presence of acid catalysts, such as $Sc(OTf)_3$ [12], NH_4Cl [13], *p*-TsOH [14], $CuCl_2$ [15] and [Bmim]PF_6 [16]. However, most of reported methods suffer from some limitations such as long reaction times, harsh reaction conditions, low yields, tedious workup and multistep reaction, some of them had to be performed in harmful organic solvent. Thus, development of a facile, atom-efficient, and eco-friendly method is highly desirable.

malonic acid is one of these homogeneous catalysts. The calcium salt of malonic acid occurs in high concentrations in beetroot, also malonic acid is inexpensive, commercial availability, nontoxic, water-solubility organoacid, has been widely used in organic reactions. Attracted our attention a due to its non-hazardous nature and easy removal from the reaction mixture, for example, via simple filtration. In this paper, we report a novel, simple and efficient procduer for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones via the condensation reaction of 2-aminobenzamide with aldehyde and ketone in the presence of amount catalytic of malonic acid in EtOH/H_2O (1:1) at room temperature (Scheme 1).



Scheme 1: synthesis of 2,3-dihydroquinazolin-4(1H)-ones

Results and discussion

The reaction of 2-aminobenzamide with benzaldehyde as a model experiment was examined in different solvents to get an insight into the solvent effect on the yields and reaction times (Table **1**). As the result, absolute ethanol and water (1:1) were preferred over other solvents because of its non-

*Corresponding author. Tel: (+98) 541 2416586, Fax: (+98) 541 2416586, E-mail: mt_maghsoodlou@yahoo.com

toxicity and low-cost, short reaction time and high yield.

Table 1: The solvent effects on time and yield of the reaction of 2-aminobezamide with benzaldehyde[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	H_2O	8	84
2	EtOH	15	70
3	MeOH	5	60
4	EtOAC	50	45
5	CH_3CN	10	79
6	**EtOH /H_2O(1:1)**	**5**	**97**

[a] Reaction condition: 2-aminobenzamide (1 mmol), benzaldehyde (1 mmol), malonic acid (10 mol%), solvent (1:1) (4 ml). [b] Isolated yield.

We tried to optimize the amount of malonic acid for the reaction between benzaldehyde and 2-aminobenzamide in EtOH/H_2O (1:1) at room temperature (Table **2**). As can be seen in table **2**, maximum yield was obtained with 10 mol% of the catalyst.

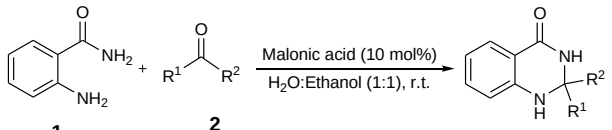
Table 2: Optimization of the amount of malonic acid for the reaction between benzaldehyd and 2-aminobenzamide[a]

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	2	12	87
2	5	9	92
3	**10**	**5**	**97**
4	15	5	97
5	20	5	95

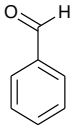
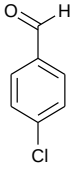
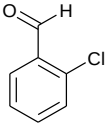
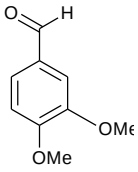
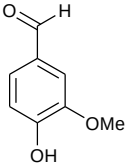
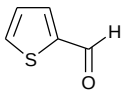
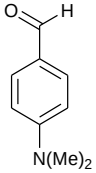
[a] Reaction condition: 2-aminobenzamide (1 mmol), benzaldehyde (1 mmol), malonic acid (X mol%), water:ethanol (1:1) (4 ml). [b] Isolated yield.

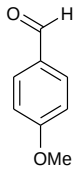
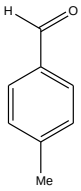
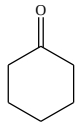
The result from the reaction of 2-aminobenzamide and various aromatic aldehydes and ketones in EtOH /H_2O shown in Table **3**. Aldehydes with electron-deficient and/or electron-releasing group reacted efficiently with 2-amino benzamide to give the corresponding of 2,3-dihydroquinazolin-4(1H)-ones in high to excellent yields.

Table 3: Synthesis of 2,3-dihydroquinazolin-4(1H)-ones by the reaction of 2- aminobenzamide with aldehydes and ketones in the presence of 10 mol% Malonic acid



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

Entry	Aldehyde or ketone	Time (min)	Product	Yield[a] (%)	Mp (°C)/ [Lit.M.P. (°C)][Ref]
1		5	**3a**	97	219/ [220-222][17]
2		4	**3b**	93	202/[203-205][18]
3		5	**3c**	98	204/[200-204][19]
4		4	**3d**	98	211/[212-214][20]
5		4	**3e**	98	218/[219-221][19]
6		37	**3f**	91	212/[211-213][1]
7		10	**3g**	81	204/[203-205][19]

8		5	**3h**	96	180/[180-182][18]
9		2	**3i**	93	224/[224-225][21]
10		8	**3j**	84	223/[224-226][22]

[a] Isolated yield.

Conclusion

In conclusion, we have reported a new efficient catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-one through cyclocondensation of 2-aminobenzamide with aromatic aldehyde and ketone using Malonic acid as catalyst. Green solvent and catalytic, mild reaction condition, short reaction time and simple workup are several advantage of this methodology.

Experimental

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT/ IR-460 plus spectrometer, respectively. All reagents and solvents obtained from Fluka and Merck were used without further purification.

*General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones **3a-j**:*

To a solution of 2-aminobenzamide **1** (1 mmol) and aldehyde or ketone **2** (1 mmol) in 4mL EtOH/H_2O (1:1), malonic acid 10mol% was added and the reaction mixture was stirred for the time indicated in Table **3**. The progress of reaction was monitored by TLC (ethyl acetate:*n*-hexane, 1:3). After completion of the reaction, solvent was removed and the solid residue was washed with EtOH. The obtained solid was collected by filtration and purified by recrystallization from EtOH. Product were characterized by comparison of their physical and spectral data with those of authentic samples.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (3c): White solid; m.p. 204 °C; IR: ν 3362, 3194, 1646, 1614, 1503, 1484, 1188, 1031, 822, 745 cm^{-1}.

2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3d): White solid; m.p. 211 °C; IR: ν 3356, 3182, 1655, 1614, 1504, 1460, 1140, 1024, 822, 759 cm^{-1}.

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (3h): White solid; m.p. 180 °C; IR: ν 3298, 3182, 1653, 1612, 1509, 1488, 1175, 1032, 835, 757 cm^{-1}.

References

[1] Yale, H. L.; Kalkstein, M. *J. Med. Chem*. **1967**, *10*, 334.

[2] Neil, G. L.; Li, L. H.; Buskirk, H. H.; Moxlcy, T. E. *Cancer Chemother*. **1972**, *56*, 163.

[3] Bonola, G.; Re, P. D; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem*. **1968**, *11*, 1136.

[4] Bolger, J. W. *US patent application US3257397A, Jun 21,* **1966**; *Chem. Abstr*. **1966**, *66*, 8933b.

[5] Boehringer Sohn, C. H. *French Patent M 2588, 1964; Chem. Abstr*. **1964**, *61*, 16075h.

[6] Alaimo, R. J.; Russel, H. E. *J. Med. Chem*. **1972**, *15*, 335.

[7] Cohen, E.; Klarberg, B.; Vaughan, J. R. *J. Am. Chem. Soc*. **1959**, *81*, 5508.

[8] Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem*. **1968**, *11*, 348.

[9] Instituto De Angeli S. P. A. *French Patent M 1893, 1964; Chem. Abstr*. **1964**, *60*, 3956.

[10] Levin, I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1141.

[11] Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem*. **2008**, *51*, 4620.

[12] Chen, J. X.; Wu, H. Y.; Su, W. K. *Chin. Chem. Lett*. **2007**, *18*, 536.

[13] Shaabani, A.; Maleki, A.; Mofakham, H. *Synth. Commun*. **2008**, *38*, 3751.

[14] Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. J.; Palermo, W. W. *J. Org. Chem*. **1969**, *34*, 887.

[15] Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett*. **2004**, *45*, 3475.

[16] Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem*. **2007**, *9*, 972.

[17] Hour, M.; Huang, L.; Kuo, S.; Xia,Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. *Med, J. Chem.* **2000**, *43*, 4479.

[18] Cai, G. P.; Xu, X. L.; Li, Z. F.; Weber, W. P.; Lu, P. *J. Heterocyclic Chem*. **2002**, *39* ,1271.

[19] Murthy, P. V.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Prasad, K. R. S.; Rao, M.V. B.; Pal, M. *Tetrahedron Lett*. **2012**, *53*, 863
[20] Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgary, G.; Mohammadi, A. A. *Tetrahedron Lett*. **2005**, *46*, 6123.
[21] Davoodnia, A.; Allameh, S.; Fakhari, A. R.; Tavakoli-Hoseini, N. *Chin. Chem. Lett*. **2010**, *21*, 550.
[22] Rostamizadeh, S.; Amani, A. M.; Mahdavinia, G. H.; Sepehrian, H.; Ebrahimi, S. *Synthesis* **2010**, 1356.