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Green and catalyst-free one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in water

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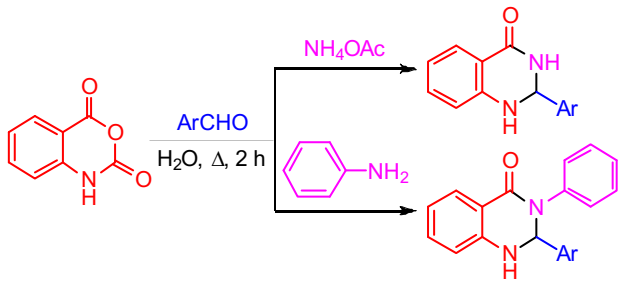


A facile and highly efficient protocol was successfully applied to synthesize mono- and disubstituted dihydroquinazolinones through a three-component coupling reaction of isatoic anhydride, aniline or ammonium acetate, and aromatic aldehydes in refluxing water with excellent yield without using any catalysts. The protocol avoids the use of hazardous solvents and chromatographic separation. The generality and functional tolerance of this convergent and environmentally benign method is demonstrated.

Keywords: aromatic aldehyde, dihydroquinazolinone, isatoic anhydride.

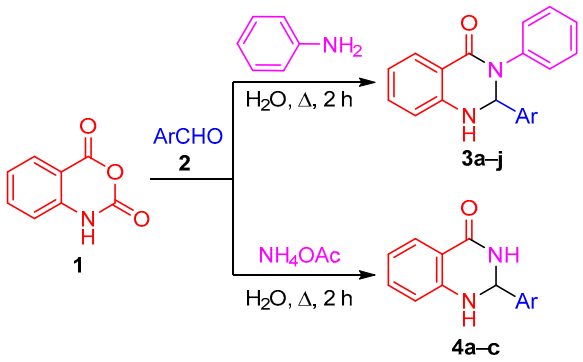
Quinazolin-4-ones are important bicyclic heterocycles which have been found to possess valuable biological and pharmacological activities involving antifungal,[1,2] analgesic,[3] antidiabetic,[4] antitumor,[5] antibacterial,[6] anticonvulsant,[7] and antihypertensive.[8] In addition, these compounds can easily be oxidized to their 4-alkynyl-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one analogs[9] which also are important pharmacologically active compounds.[10,11]

Due to the significant interest in 2,3-dihydroquinazolin-4(1*H*)-ones, several synthetic strategies[12–14] have been developed for the preparation of substituted dihydroquinazolin-4(1*H*)-ones. The formation of these compounds generally can be accomplished by condensation of isatoic anhydride, aldehydes, and amines in the presence of montmorillonite K-10,[15] silica sulfuric acid,[16] zinc(II) perfluorooctanoate,[17] MCM-41-SO_3H,[18] Amberlyst-15,[19] $Ga(OTf)_3$,[20] *p*-toluenesulfonic acid,[21] $Al(H_2PO_4)_3$,[22] SiO_2–$FeCl_3$,[23] $SnCl_2$,[24] ceric ammonium nitrate,[25] silica-bonded *S*-sulfonic acid,[26] and Al/Al_2O_3,[27] Fe_3O_4 nanoparticles,[28] metal complexes with multi-walled carbon nanotubes,[29] silica-supported ceric ammonium nitrate,[30] SiO_2-$ZnCl_2$,[31] $KAl(SO_4)_2 \cdot 12H_2O$,[32] TiO_2 nanoparticles,[33] and ionic liquids.[34] However, some reported methods have certain disadvantages, such as tedious process, long reaction times, harsh reaction conditions, high reaction temperature, and low yields with the use of various catalysts. Therefore, the development of a clean, high yielding, and eco-friendly approach is highly desirable.

Due to growing environmental concerns, carrying out multicomponent reactions (MCRs) in water has become highly desirable, and several reports of organic synthesis in water have appeared during the past decade.[35–38] As the most abundant, cheapest, and environmentally friendly solvent, water offers several practical advantages over conventional organic solvents such as easy availability, low costs, and safe handling.[39] Furthermore, besides having a unique reactivity and selectivity, water also offers an easy separation. The above advantages have been attributed to many factors, including the hydrophobic effect, enhanced hydrogen bonding in the transition state, and the high cohesive energy density of water.[39]

Due to our interest in developing multicomponent reactions,[40–42] we report here an efficient procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through a one-pot three-component condensation of isatoic anhydride,

Table 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **3a**–**j** and **4a**–**c**



Entry	Ar	Product	Yield, %	Mp, °C	
				Found	Reported
1	Ph	**3a**	88	213–214	214–215[20]
2	4-MeC$_6$H$_4$	**3b**	89	212–213	213–214[45]
3	4-MeOC$_6$H$_4$	**3c**	87	213–215	218–220[44]
4	3-O$_2$NC$_6$H$_4$	**3d**	88	186–188	186–188[15]
5	4-O$_2$NC$_6$H$_4$	**3e**	90	191–193	195–197[32]
6	4-BrC$_6$H$_4$	**3f**	85	216–218	221–223[30]
7	4-FC$_6$H$_4$	**3g**	87	231–233	235–238[23] 224–226[48]
8	2-HO-3-MeOC$_6$H$_3$	**3h**	85	204–206	–
9	2,6-Cl$_2$C$_6$H$_3$	**3i**	87	218–220	234–236[43]
10	2-Naphthyl	**3j**	85	229–230	243[44]
11	Ph	**4a**	88	227–228	225–226[47]
12	4-MeC$_6$H$_4$	**4b**	89	230–232	233–234[20]
13	4-MeOC$_6$H$_4$	**4c**	90	187–189	192–193[46]

aromatic aldehyde, and amine in aqueous medium. To the best of our knowledge, there are no literature examples of the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in water under catalyst-free conditions.

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, we initiated our studies by the reaction of isatoic anhydride, benzaldehyde, and aniline in water at room temperature. When the reaction was carried at room temperature in the absence of catalyst, it was not complete even after a longer time (10 h), and the resulting yield was poor. To study the temperature effect, the reaction was carried out at different temperatures. It was found that under reflux conditions an excellent yield of the corresponding product was achieved, and the reaction required 2 h for completion.

With these optimized conditions in hand, the reaction of isatoic anhydride (**1**) with a wide range of aromatic aldehydes **2** and either aniline or ammonium acetate was examined to explore the scope and generality of the present protocol for the synthesis of various 2,3-dihydroquinazolin-4(1*H*)-ones **3a**–**j** and **4a**–**c**, respectively (Table 1). Thus, we were in position to investigate the scope and efficiency of this reaction and to study the effect of substituents on the product formation. It was found that this method had good tolerance for various substitutions. It should be noted that the electronic nature and position of substituent on the phenyl rings did not show strong influence on the reaction, and the products in all cases were obtained in high to excellent yields (84–90%). After completion of the reaction, water was decanted, and the pure product was conveniently obtained by recrystallization from ethanol. The products **3a**–**g**,**i**,**j** and **4a**–**c** have been described before, while compound **3h** is reported for the first time.

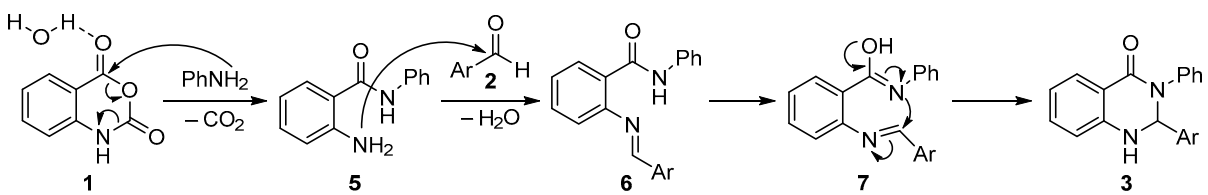
According to evolution of the reaction conditions, a possible mechanism for the formation of products **3a**–**j** is presented in Scheme 1. It is proposed that, at first, water acts as a hydrogen bond donor to activate carbonyl group of isatoic anhydride **1**. Then, as a result of ring opening and decarboxylation caused by nucleophilic attack of amine to the carbonyl group intermediate anthranilamide **5** is formed. Subsequently, the reaction of activated aldehyde with anthranilamide **5** proceeds to afford the imine intermediate **6**. The tautomerization of amide group and activation of the imine moiety in the intermediate **6** can be catalyzed in water by formation of hydrogen bonding to give the intermediate **7**. This intermediate can convert to the title product **3** by cyclization *via* intramolecular nucleophilic attack of carboximidate nitrogen on imine carbon. The pathway to compounds **4a**–**c** would be analogous.

In conclusion, we described a simple, highly efficient, and straightforward protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in water under reflux conditions. Furthermore, the protocol offers several advantages including facile experimental procedure without using catalysts and toxic solvents, simple work-up and purification, and high isolated yields of the pure products. The simplicity of the procedure and predictable low costs makes it a useful and attractive strategy for the synthesis of dihydroquinazolinones.

Experimental

IR spectra were recorded on a Shimadzu 4300 spectrophotometer in KBr. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer

Scheme 1



(300 and 75 MHz, respectively) in DMSO-d_6. The internal standard for the ^{1} and ^{13}C NMR spectra was TMS. Mass spectra (electron impact ionization, 70 eV) were obtained with an Agilent technologies HP 5973 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-Rapid elemental analyzer. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. All commercially available chemicals and reagents were used without further purification.

Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives 3a–j and 4a–c (General method). A 25-ml round-bottomed flask was charged with isatoic anhydride (**1**) (0.163 g, 1.0 mmol), aniline (0.093 g, 1.0 mmol) or ammonium acetate (0.077 g, 1.0 mmol), aromatic aldehyde **2** (1.0 mmol), and water (10 ml). The mixture was stirred under reflux for 2 h. Afterwards, the reaction mixture was cooled to room temperature, and water was decanted to afford the crude product which was recrystallized from ethanol to get the pure final product.

2-(2-Hydroxy-3-methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3h). Yield 0.29 g (85%). IR spectrum, , cm^{-1}: 3386, 3191, 3059, 1643, 1608, 1492, 1431, 1410, 1279, 1047. ^{1}H NMR spectrum, , ppm (*J*, Hz): 3.73 (3H, s, OCH_3); 6.39 (1H, s, CH); 6.65–6.85 (5H, m, H Ar); 7.08 (1H, s, NH); 7.13–7.32 (6H, m, H Ar); 7.71 (1H, d, *J* = 9.3, H Ar); 9.13 (1H, s, OH). ^{13}C NMR spectrum, , ppm: 56.2 (OCH_3); 68.4 (NHCH); 112.0; 115.3; 115.4; 117.7; 118.8; 119.0; 119.2; 126.5; 127.4; 128.2; 129.0; 134.0; 141.3; 143.4; 147.0; 148.0; 162.9 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 346 $[M]^+$ (100), 254 (55), 223 (76), 210 (23), 196 (28), 183 (26), 167 (25), 120 (48), 92 (24), 77 (34). Found, %: C 72.90; H 5.16; N 8.13. $C_{21}H_{18}N_2O_3$. Calculated, %: C 72.82; H 5.24; N 8.09.

2-(2,6-Dichlorophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3i). Yield 0.32 g (87%). IR spectrum, , cm^{-1}: 3249, 3050, 1626, 1590, 1563, 1540, 1457, 1435, 1315, 1195. ^{1}H NMR spectrum, , ppm (*J*, Hz): 6.58–6.61 (2H, m, H Ar, CH); 7.13–7.37 (10H, m, H Ar, NH); 7.62 (2H, d, *J* = 9.0, H Ar). ^{13}C NMR spectrum, , ppm: 70.8 (NHCH); 112.8; 113.5; 116.7; 127.7; 127.9; 128.0; 128.8; 129.5; 131.4; 133.5; 134.2; 135.6; 139.4; 147.4; 162.3 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 372 $[M(^{37}Cl,^{37}Cl)]^+$ (7), 370 $M(^{37}Cl, ^{35}Cl)]^+$ (25), 368 $[M(^{35}Cl,^{35}Cl)]^+$ (25), 276 (81), 223 (100), 186 (10), 120 (15), 105 (27), 77 (34). Found, %: C 65.10; H 3.83; N 7.63. $C_{20}H_{14}Cl_2N_2O$. Calculated, %: C 65.06; H 3.82; N 7.59.

2-(2-Naphthyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (3j). Yield 0.29 g (85%). IR spectrum, , cm^{-1}: 3298, 3057, 1632, 1610, 1488, 1444, 1310, 1258, 1116. ^{1}H NMR spectrum, , ppm (*J*, Hz): 6.45 (1H, s, CH); 6.66–6.76 (2H, m, H Ar); 7.13–7.86 (15H, m, H Ar, NH). ^{13}C NMR spectrum, , ppm: 73.2 (NHCH); 115.1; 115.7; 118.0; 124.9; 126.0; 126.5; 126.8; 126.9 (2C); 127.9; 128.4; 128.7; 129.0; 132.6; 133.1; 134.2; 138.4; 141.2; 146.9; 147.0; 162.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 350 $[M]^+$ (55), 258 (100), 223 (69), 202 (25), 153 (7), 130 (16), 105 (11), 92 (12), 77 (24). Found, %: C 82.25; H 5.18; N 8.07. $C_{24}H_{18}N_2O$. Calculated, %: C 82.26; H 5.12; N 7.99.

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References

1. Cox, R. J.; O'Hagan, D. *J. Chem. Soc. Perkin*, *Trans. 1* **1991**, *1*, 2537.
2. Bartroli, J.; Turmo, E.; Alguero, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1998**, *41*, 1869.
3. El-Sabbagh, O. I.; Ibrahim, S. M.; Baraka, M. M.; Kothayer, H. *Arch. Pharm.* **2010**, *343*, 274.
4. Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C.-Y.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X.-G.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A.; Tang, W.; Wang, L.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. *J. Med. Chem.* **2007**, *50*, 5202.
5. Hour, M.-J.; Huang, L.-J.; Kuo, S.-C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 4479.
6. Alaimo, R. J.; Russell, H. E. *J. Med. Chem.* **1972**, *15*, 335.
7. White, D. C.; Greenwood, T. D.; Downey, A. L.; Bloomquist, J. R.; Wolfe, J. F. *Bioorg. Med. Chem.* **2004**, *12*, 5711.
8. Abdel-Jalil, R. J.; Volter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475.
9. Lopez, S. E.; Rosales, M. E.; Urdaneta, N.; Godoy, M. V.; Charris, J. E. *J. Chem. Res.* **2000**, 258.
10. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bachheler, L. T.; Diamond, S.; Jeffey, K.; Trainor, S.; Anderson, G. L.; Erickson-Vitanen, P. S. *J. Med. Chem.* **2000**, *43*, 2019.
11. Liu, J. F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241.
12. Magyar, T.; Miklós, F.; Lázár, L.; Fülöp, F. *Chem. Heterocycl. Compd.* **2015**, *50*, 1464. [*Khim. Geterotsikl. Soedin*. **2014**, 1590.]
13. Fozooni, S.; Firoozi, H. *Chem. Heterocycl. Compd.* **2015**, *51*, 340. [*Khim. Geterotsikl. Soedin*. **2015**, *51*, 340.]
14. Wang, M.; Zhang, T. T.; Gao, J. J.; Liang, Y. *Chem. Heterocycl. Compd.* **2012**, *48*, 897. [*Khim. Geterotsikl. Soedin*. **2012**, 965.]
15. Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. *Synth. Commun.* **2006**, *36*, 2287.
16. Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Agheb, M.; Heydari, S. *Catal. Commun.* **2008**, *9*, 785.
17. Wang, L. M.; Hu, L.; Shao, J. H.; Yu, J. J.; Zhang, L. *J. Fluorine Chem.* **2008**, *129*, 1139.
18. Rostamizadeh, S.; Amani, A. M.; Mahdavinia, G. H.; Sepehrian, H.; Ebrahimi, S. *Synthesis* **2010**, 1356.
19. Surpur, M. P.; Singh, P. R.; Patil, S. B.; Samant, S. D. *Synth. Commun.* **2007**, *37*, 1965.
20. Chen, J. X.; Wu, D. Z.; He, F.; Liu, M. C.; Wu, H. Y.; Ding, J. C.; Su, W. K. *Tetrahedron Lett.* **2008**, *49*, 3814.
21. Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. *Synthesis* **2006**, 344.
22. Shaterian, H. R.; Oveisi, A. R.; Honarmand, M. *Synth. Commun.* **2010**, *40*, 1231.
23. Ghashang, M.; Azizi, K.; Moulavi-Pordanjani, H.; Shaterian, H. R. *Chin. J. Chem.* **2011**, *29*, 1617.
24. Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 6941.

25. Baghbanzadeh, M.; Dabiri, M.; Salehi, P. *Heterocycles* **2008**, *75*, 2809.
26. Niknam, K.; Mohammadizadeh, M. R.; Mirzaee, S. *Chin. J. Chem.* **2011**, *29*, 1417.
27. Kassaee, M. Z.; Rostamizadeh, S.; Shadjou, N.; Motamedi, E.; Esmaeelzadeh, M. *J. Heterocycl. Chem.* **2010**, *47*, 1421.
28. Zhang, Z. H.; Lu, H. Y.; Yang, S. H.; Gao, J. W. *J. Comb. Chem.* **2010**, *12*, 643.
29. Safari, J.; Gandomi-Ravandi, S. *J. Mol. Struct.* **2014**, *1072*, 173.
30. Dindulkar, S. D.; Oh, J.; Arole, V. M.; Jeong, Y. T. *C. R. Chim.* **2014**, *17*, 971.
31. Ghashang, M. *Orient. J. Chem.* **2012**, *28*, 1213.
32. Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgary, G.; Mohammadi, A. A. *Tetrahedron Lett.* **2005**, *46*, 6123.
33. Bharathi, A.; Roopan, S. M.; Kajbafvala, A.; Padmaja, R. D.; Darsana, M. S.; Kumari, G. N. *Chin. Chem. Lett.* **2014**, *25*, 324.
34. Darvatkar, N. B.; Bhilare, S. V.; Deorukhkar, A. R.; Raut, D. G.; Salunkhe, M. M. *Green Chem. Lett. Rev.* **2010**, *3*, 301.
35. Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751.
36. Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
37. Kumaravel, K.; Vasuki, G. *Curr. Org. Chem.* **2009**, *13*, 1820.
38. *Water in Organic Synthesis*; Workbench Edition (Science of Synthesis); Kobayashi, S., Ed.; Thieme: Stuttgart, New York, 2012.
39. Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.
40. Olyaei, A.; Gesmati, F.; Sadeghpour, M.; Shams, B.; Alizadeh, M. *Synth. Commun*. **2012**, *42*, 1650.
41. Olyaei, A.; Karbalaei Karimi, M.; Razeghi, R. *Tetrahedron Lett.* **2013**, *54*, 5730.
42. Olyaei, A., Ghodrat Alidoust, M. *Synth. Commun*. **2015**, *45*, 94.
43. Karimi-Jaberi, Z.; Arjmandi, R. *Monatsh. Chem.* **2011**, *142*, 631.
44. Ghorbani-Choghamarani, A.; Taghipour, T. *Lett. Org. Chem.* **2011**, *8*, 470.
45. Santra, S.; Rahman, Anupam Roy, M.; Majee, A.; Hajra, A. *Catal. Commun.* **2014**, *49*, 52.
46. Chen, J. X.; Wu, D. Z.; He, F.; Liu, M. C.; Wu, H. Y.; Ding, J. C.; Su, W. K. *Tetrahedron Lett.* **2008**, *49*, 3814.
47. Rostamizadeh, S.; Amani, A. M.; Aryan, R.; Ghaieni, H. R.; Shadjou, N. *Synth. Commun.* **2008**, *38*, 3567.
48. Niknam, K.; Jafarpour, N.; Niknam, E. *Chin. Chem. Lett.* **2011**, *22*, 69.