Rapid Synthesis of 2-Substituted-2,3-dihydro-4(1*H*)-quinazolinones using Boric Acid or Sodium Dihydrogen Phosphate under Solvent-Free Conditions

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ABSTRACT

Two efficient and convenient methods have been described for synthesis of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinone derivatives by one-pot condensation of 2-anthranilamide with aldehydes or ketones in the presence of a catalytic amount of boric acid or sodium dihydrogen phosphate under solvent-free conditions. The attractive features of these processes are short reaction times, easy isolation of products, excellent yields and an environmental friendly procedure.

KEYWORDS

Dihydroquinazolinones, boric acid, sodium dihydrogen phosphate, 2-anthranilamide, solvent-free synthesis.

1. Introduction

Dihydroquinazolinones are of considerable interest as they exhibit biological properties, such as antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating behaviour.[1–6] Furthermore, the prevalence of quinazolinone skeleton in various natural products[7–9] has instituted several efforts to develop synthetic approaches to the quinazolinone alkaloids.[10,11] In addition, a variety of synthetic routes have been reported for the synthesis of quinazolinone derivatives.[12–14] Of these, the condensation of 2-anthranilamide with aldehydes or ketones is the most convenient methods for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones.[14b] Various acid catalysts, such as ionic liquid,[15] ammonium chloride,[16] tetrabutylammonium bromide,[17] trifluoroethanol,[18a] acetic acid[18b] and sulfamic acid[19] have been used to promote this reaction. However, many of these methods involve extended reaction times, the use of costly reagents or toxic organic solvents and also require tedious work-up procedures. Some catalysts had to be prepared in advance and their preparation required special effort. Therefore, the development of simple and efficient methods for the synthesis of quinazolinones is of great importance.

Because of our interest in studying environmentally friendly procedures for several important organic transformations,[20–22] we have recently developed an acetic acid-promoted, one-pot synthesis of 2,3-dihydro-4(1*H*)-quinazolinones.[23] We report here two new and very convenient procedures for the condensation of 2-anthranilamide with structurally diverse aromatic aldehydes or ketones to the corresponding 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones using catalytic amounts of boric acid or sodium dihydrogen phosphate under solvent-free conditions

2. Results and Discussion

Boric acid (H_3BO_3) is a useful and environmentally benign catalyst which can effectively promote some organic reactions like the aza-Michael addition,[24] the Biginelli reaction,[25] the Mannich reaction[26] and synthesis of alkylidene bisamides,[27] dibenzoxanthenes[21] and α-aminophosphonates.[22] It offers milder conditions relative to common mineral acids. Boric acid is a readily available and inexpensive reagent and can conveniently be added and later removed from the reaction mixture. Hence, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones.

To optimize the reaction conditions, the reaction of benzaldehyde with 2-anthranilamide was used as a model reaction. Reactions using different conditions and various molar ratios of substrates in the presence of boric acid revealed that the best conditions were solvent-free at 120 °C and with a molar ratio of 2-anthranilamide/aldehyde/boric acid of 1:1:0.2. After completion of the reaction, the catalyst (boric acid) can easily be separated from the reaction mixture by washing the product with water.

To show the generality of the present method the optimized system was utilized for the synthesis of other derivatives. Various examples illustrating this novel and general method for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones are summarized in Table 1 (Method A). A verity of different functionalities present in the aryl aldehydes, such as halogen, methoxy, hydroxyl, cyano and nitro groups were tolerated (see Table 1). The reaction can also proceed with ketones and provide the target products in reasonable yield (Table 1, entries 15, 16). In all these cases, the corresponding 2,3-dihydro-4(1*H*)-quinazolinones were obtained in good yields at 120 °C under solvent-free conditions without formation of any side products. It is important to note that the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones could not be achieved in the absence of the boric acid catalyst. All products are known compounds and structures of them were verified by comparison with their known physical and spectral (NMR and IR) data.[17–21]

Moreover, we turned our attention to other catalysts for this reaction, such as sodium dihydrogen phosphate (NaH_2PO_4). We previously reported sodium dihydrogen phosphate as a

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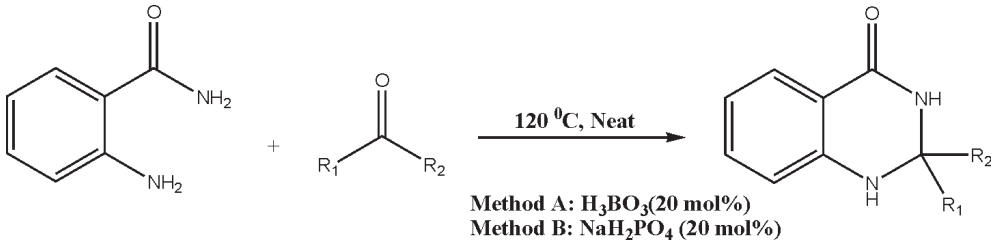

Scheme 1

Table 1 Synthesis of 2,3-dihydro-4(1*H*)-quinazolinones in the presence of boric acid or sodium dihydrogen phosphate.

Entry	Aldehyde/ketone	Method A [a]		Method B [b]		m.p./°C	Ref.
		Time/min	Yield/%	Time/min	Yield/%		
1	Benzaldehyde	3	81	5	75	216–218	15
2	4-Cyanobenzaldehyde	3	85	15	81	250–253	18
3	3-Nitrobenzaldehyde	3	82	5	80	208–210	19
4	4-Nitrobenzaldehyde	3	80	5	81	190–192	28
5	2-Chlorobenzaldehyde	3	88	5	75	208–210	28
6	4-Chlorobenzaldehyde	3	85	15	50	192–202	19
7	2,4-Dichlorobenzaldehyde	5	81	15	50	172–174	28
8	2,6-Dichlorobenzaldehyde	5	87	5	80	167–170	–
9	4-Methoxybenzaldehyde	3	92	12	77	192–194	19
10	2-Methoxybenzaldehyde	3	73	15	50	209–212	17
11	4-Methylbenzaldehyde	3	86	5	73	230–233	19
12	4-Fluorobenzaldehyde	3	82	5	83	201–203	18
13	4-Bromobenzaldehyde	3	86	15	78	280–285	17
14	4-Hydroxybenzaldehyde	3	83	–	–	298–300	28
15	Cyclohexanone	3	87	5	82	215–218	16
16	Cyclopentanone	3	77	15	78	257–259	16

[a] Method A: 20 mol % boric acid.
[b] Method B: 20 mol% sodium dihydrogen phosphate.

catalyst for the synthesis of α-aminophosphonates.[20] Sodium dihydrogen phosphate is readily available and inexpensive and can conveniently be introduced and removed from the reaction mixture. Gratifyingly, a good yield of product was obtained by treatment of benzaldehyde with 2-anthranilamide in the presence of catalytic sodium dihydrogen phosphate under solvent-free conditions. To show the generality and scope of the sodium dihydrogen phosphate-promoted 2,3-dihydro-4(1*H*)-quinazolinones synthesis, the reaction was examined with various structurally diverse aldehydes or ketones (Table 1, method B). However, 4-hydroxybenzaldehyde failed to react (Table 1, entry 14). It can be suggested that the strongly electron donating hydroxy group diminishes reactivity of the aldehyde.

The reaction proceeds via condensation of 1 mol of aldehyde or ketone with 1 mol of 2-anthranilamide followed by elimination of water to form the corresponding 2,3-dihydro-4(1*H*)-quinazolinones as has been suggested earlier.[16–19] Table 2 compares our results for the synthesis of 2,3-dihydro-2-phenyl-4(1*H*)-quinazolinone through the condensation of 2-anthranilamide with benzaldehyde with the results of different catalysts and reaction conditions obtained by other groups. As shown in Table 2, the yield/time ratio of our present method is better or comparable with others.

3. Conclusion

In conclusion this paper describes two convenient and efficient processes for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones by one-pot reaction of aldehydes or ketones and 2-anthranilamide in the presence of catalytic boric acid or sodium dihydrogen phosphate. These methods offer some advantages in terms of simplicity of performance, solvent-free conditions, low cost, and it follows along the line of green chemistry. The catalysts are readily available and inexpensive and can be conveniently manipulated in the reaction. We believe this procedure is convenient, inexpensive and environmentally-friendly process for the synthesis of 2,3-dihydro-4(1*H*)-quinazolinones with potential biological application.

Table 2 Comparison of efficiency of various catalysts in the synthesis of 2,3-Dihydro-2-phenyl-4(1H)-quinazolinone.

Entry	Catalyst	Condition	Time/min)	Yield/%	Ref.
1	[Bmim]PF6	75 °C	35	89	15
2	NH_4Cl (5 mol%)	EtOH, rt	15	92	16
3	Bu_4NBr (40 mol%)	N_2 atmosphere, 100 °C	90	82	17
4	2,2,2-trifluoroethanol	reflux	90	90	18
5	sulfamic acid (10 mol%)	MeOH, rt	20	89	19
6	Boric acid (20 mol%)	Solvent-free-120 °C	3	81	This work

4. Experimental

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

A mixture of 2-anthranilamide (1 mmol), aldehyde/ketone (1 mmol), and boric acid or sodium dihydrogen phosphate (20 mol %) was stirred at 120 °C for the appropriate time indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane). After completion of the reaction, a solid was obtained. It was washed with water and purified by recrystalization from ethanol to afford pure products.

*2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one* (entry 1): white crystals, m.p. 216–218 °C, IR (KBr) cm^{-1}: 3303, 3184, 3059, 2933, 1656, 1611, 1511, 1439; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 5.73 (1H, s, CH), 6.65–6.74 (2H, m, ArH), 7.08 (1H, s, NH), 7.22–7.60 (7H, m, ArH), 8.25 (1H, s, NH–CO).

*2,3-Dihydro-2-(2,6-dichlorophenyl)quinazolin-4(1*H*)-one* (entry 8): white crystals , m.p. 167–170 °C, IR (KBr) cm^{-1}: 3274, 1685, 1613, 1485; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 6.57–6.65 (2H, m, ArH), 6.74 (1H, s, CH), 6.98 (1H, s, NH), 7.17–7.23 (1H, m, ArH), 7.37–7.60 (4H, m, ArH), 8.10 (1H, s, NH–CO). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 64.8, 114.0, 127.6, 127.8, 130.2, 130.3, 131.5, 132.9, 133.8, 133.9, 135.8, 138.4, 139.8, 163.2. Anal. Calcd for $C_{14}H_{10}Cl_2N_2O$: C, 57.36; H, 3.44; N, 9.56; Found: C, 57.23; H, 3.39; N, 9.50.

*2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one* (entry 9): white crystals, m.p. 192–194 °C, IR (KBr) cm^{-1}: 3297, 3181, 3053, 2932, 1670, 1609, 1572, 1514, 1463; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.72 (3H, s, CH_3), 5.68 (1H, s, CH), 6.62–6.73 (2H, m, ArH), 6.90–6.98 (3H, m, NH and ArH), 7.18–7.25 (1H, m, ArH), 7.39 (2H, d, J =8.25, ArH), 7.59 (1H, d, J =7.75, ArH), 8.15 (1H, s, NH–CO).

*2-Spirocyclopentyl-2,3-dihydroquinazolin-4(1*H*)-one* (entry 16): white crystals , m.p. 257–259 °C, IR (KBr) cm^{-1}: 3163, 2939, 1639, 1614, 1516, 1483, 1429, 1383, 1322; ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.63–1.65 (4H, m, $2CH_2$), 1.74–1.76 (4H, m, $2CH_2$), 6.57–6.71 (3H, m, NH and ArH), 7.15–7.21 (1H, m, ArH), 7.59(1H, d, J = 7.5, ArH), 8.06 (1H, s, NH–CO); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ: 22.4, 38.92, 77.5, 114.7, 115, 117, 127.6, 133.4, 147.9, 163.9.

References

1 J.F. Wolf, T.L Rathman, M.C. Sleevi, J.A. Campbell and T.D. Greenwood, *J. Med. Chem.*, 1990, **33**, 161.

2 J.K. Pasia, M. Field, J. Hinton, K. Meecham, J. Pablo, R. Pinnock, B.D, Roth, L. Singh, N. Suman-Chauhan, B.K, Trivedi and L. Webdale, *J. Med. Chem.*, 1998, **41**, 1042.

3 Y. Xia, Y.Z. Yang, M.J. Hour, S.C. Kuo, P. Xia, K.F. Bastow, Y. Nakanishi, P. Nampoothiri, T. Hackl, E. Hamel and K.H. Lee, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1193.

4 G.L. Neil, L.H. Li, H.H. Buskirk and T.E. Moxley, *Cancer Chemother.*, 1972, **56**, 163.

5 N.M. Abdel Gawad, H.H. Georgey, R.M. Youssef and N.A. El-Sayed, *Eur. J. Med. Chem.*, 2010, **45**, 6058.

6 J.L. Levin, P.S. Chan, T. Bailey, A.S. Katocs and A.M. Venkatesan, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1141.

7 R.P. Maskey, M. Shaaban, I. Gruen-Wollny and H. Laatsch, *J. Nat. Prod.*, 2004, **67**, 1131.

8 G.P. Michel, *Nat. Prod. Rep.*, 2004, **21**, 650.

9 Z.Z. Ma, Y. Hano, T. Nomura and Y.J. Chen, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1193.

10 W.R. Bowman, M.R.G. Elsegood, T. Stein and G.W. Weaver, *Org. Biomol. Chem.*, 2007, **5**, 103.

11 U.A. Kishirsagar and N.P. Argade, *Org. Lett.*, 2010, **12**, 3716.

12 A.Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659.

13 X.V. Liu, H. Fu, Y.Y. Jiang and Y.F. Zhao, *Angew. Chem. Int. Ed.*, 2009, **48**, 348.

14 a) Z.H. Zhang, Y.H. Lu, S.H. Yang and J.W. Gao, *J. Comb. Chem.*, 2010, **12**, 643. b) B.V.S. Reddy, A. Venkateswarlu, Ch. Madan and A. Vinu, *Tetrahedron Lett.*, 2011, **52**, 1891.

15 J. Chen, W. Su, H. Wu, M. Liu and C. Jin, *Green Chem.*, 2007, **9**, 972.

16 A. Shaabani, A. Maleki, H and Mofakham, *Synth. Commun.*, 2008, **38**, 3751.

17 A. Davoodnia, S. Allameh, A.R. Fakhari and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, 2010, **21**, 550.

18 a) R.A. Oila, B.L. Xu and Y.H. Wang, *Chin. Chem. Lett.*, 2007, **18**, 656. b) R.A. Bunce and B. Nammalwar, *J. Heterocycl. Chem.* 2011, **48**, 991.

19 A. Rostami , A. Tavakoli, *Chin. Chem. Lett.*, 2011, **22**, 1317.

20 Z. Karimi-Jaberi, M.Amiri and N. Sadeghi, *Synth. Commun.*, 2010, **40**, 2948.

21 Z. Karimi-Jaberi and M. Keshavarzi, *Chin. Chem. Lett.*, 2010, **21**, 547.

22 Z. Karimi-Jaberi and M. Amiri, *Heteroatom Chem.*, 2010, **21**, 96.

23 Z. Karimi-Jaberi and R. Arjmandi, *Monatsh. Chem.*, 2011, **142**, 631.

24 M.K, Chaudhuri and S. Hussain, M.L, Kantam, B. Neelima, *Tetrahedron Lett.*, 2005, **46**, 8329.

25 S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi and X. Wang, *Tetrahedron Lett.*, 2003, **44**, 6153.

26 C. Mukhopadhyay, A. Datta and R.J. Butcher, *Tetrahedron Lett.*, 2009, **50**, 4246.

27 G. Harichandran, S.D. Amalraj and P. Shanmugam, *J. Iran. Chem. Soc.*, 2011, **8**, 298.

28 M. Wang, T.T. Zhang and Z.G. Song, *Chin. Chem. Lett.*, 2011, **22**, 427.