Monatsh Chem
DOI 10.1007/s00706-016-1804-9

ORIGINAL PAPER

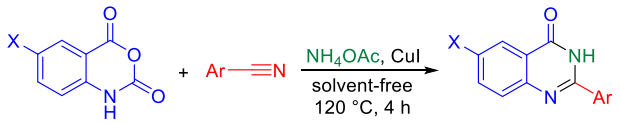
Solvent-free copper-catalyzed three-component synthesis of 2-substituted quinazolin-4(3*H*)-ones

Mehdi Soheilizad[1] · **Shakiba Soroosh**[2] · **Rahim Pashazadeh**[1]

Received: 26 April 2016 / Accepted: 13 June 2016

Abstract A novel and efficient approach for the synthesis of quinazoline-4(3*H*)-ones through a one-pot copper-catalyzed three-component reaction of isatoic anhydrides, aryl nitriles, and ammonium acetate under solvent-free conditions in good yields is described.

Graphical abstract



Keywords Ammonium acetate · Copper (I) iodide · Isatoic anhydride · Nitriles · Quinazoline-4(3*H*)-one

Introduction

Quinazoline-4(3*H*)-one core is an important class of biologically active nitrogen-containing heterocyclic scaffold with ample medicinal activities, including anti-inflammatory [1, 2], anti-microbial [3, 4], anticancer [5, 6], antidiabetic [7], anti-ulcer [8], anti-bacterial [9, 10], anti-convulsant [11, 12], anti-virus [13], and anti-cytotoxin [14].

Due to a wide range of medicinal applications, the development of novel and efficient protocols for the synthesis of quinazoline-4(3*H*)-ones has been made more valuable. As a result, numerous synthetic routes for the preparation of quinazolinone derivatives reported in the literature include the reaction of isatoic anhydride with amidoximes catalyzed by $FeCl_3$ [15], domino reaction of alkyl halides and anthranilamides catalyzed by CuBr [16], *p*-TSA-catalyzed cyclization of 2-aminobenzamides and aldehydes followed by oxidative dehydrogenation with $PhI(OAc)_2$ [17], reaction of 2-nitrobenzamides with aldehydes via in situ reduction of nitro group by $Na_2S_2O_4$ [18], the C–C bond cleavage of 2,2-disubstituted 1,2,3,4-tetrahydroquinazolinone by CuBr/air catalytic system [19], three-component reaction of isatoic anhydride, primary amines, and benzyl halides under Kornblum oxidation conditions [20], copper-catalyzed domino Ullmann-type coupling and aerobic oxidative C–H amidation of 2-halobenzamides and (aryl)methanamines [21], coupling/condensative cyclization of 2-haloarylcarbox-amides with imidamides catalyzed by CuI [22], Pd-catalyzed cyclocarbonylation of 2-iodoanilines with imidoyl chlorides [23], condensation of anthranilic acids, carboxylic acids, and amines under microwave conditions [24], reaction of isatoic anhydride, orthoesters, and primary amines catalyzed by silica sulfuric acid [25], CuO nanoparticle-catalyzed three-component reaction of isatoic anhydride, aldehydes, and amine or ammonium under ultrasound irradiation [26], and reaction between 2-aminobenzamides and aryl halides via a palladium-catalyzed isocyanide insertion/cyclization sequence [27], and so on [28–33].

Albeit the reported procedures are useful approaches for the synthesis of quinazolinones, most of them suffer from

Electronic supplementary material The online version of this article (doi:10.1007/s00706-016-1804-9) contains supplementary material, which is available to authorized users.

✉ Mehdi Soheilizad
m.soheilizad@yahoo.com

[1] School of Chemistry, College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran

[2] Department of Chemistry, Faculty of Science, Central Tehran Branch, Islamic Azad University, Tehran, Iran

Published online: 16 August 2016

remarkable limitations, such as harsh reaction conditions, long reaction times, low yields of the products, difficult work-up and use of expensive and toxic catalysts, reagents, or media. Therefore, the development of simple and efficient approaches for the synthesis of quinazolinone derivatives is strongly favorable. Hence, we herein describe a novel and straightforward protocol for the synthesis of quinazoline-4(3*H*)-ones through a copper-catalyzed three-component condensation of isotaic anhydrides, aryl nitriles, and ammonium acetate. Although a large number of functional groups and modifications have been successfully explored, to the best of our knowledge, there has been no report concerning the use of nitriles as the starting materials for the preparation of quinazoline-4(3*H*)-ones.

Result and discussion

In continuation of our studies on preparation of nitrogen-containing organic compounds [34–38], herein, we report a novel and efficient solvent-free approach for the synthesis of quinazoline-4(3*H*)-ones **3**, through a three-component condensation of isatoic anhydride **1**, aryl nitriles **2**, and ammonium acetate in the present of CuI as catalyst under solvent-free conditions (Scheme 1).

In begin our r esearch, preparation of 2-phenylquinazolin-4(3*H*)-one (**3a**) was investigated as model reaction (Table 2, entry 1). Also, the influence of various factors, such as the ammonium salts, catalyst, temperature, time, and reaction medium, was evaluated (Table 1). First, to find a convenient reaction conditions, the model reaction was carried out using 1 equivalent of NH_4OAc, in the absence and presence of CuI as catalyst, at 120 °C under solvent-free conditions (entries 1 and 2). As shown in Table 1, in the absence of CuI, no product was formed (entry 1), but in the presence of CuI (10 mol %), the reaction took place with 27 % yield (entry 2). Next, to optimize the amount of NH_4OAc, the model reaction was carried out using two to five equivalents of NH_4OAc, and CuI (10 mol %), at 120 °C under solvent-free conditions (entries 3–6). The best yield of **3a** (87 %) was obtained with 4 equivalent of NH_4OAc (entry 5). Then, to find the best amount of CuI catalyst, the model reaction was examined by 5 and 15 mol % of CuI (entries 7 and 8), and finally, we found that 10 mol % of CuI gave the best result (entry 5). Also, other Cu source catalysts, such as $Cu(OAc)_2$, CuO, Cu_2O, $CuCl_2$, and CuBr, could not enhance the yield of desire product (entries 9–13). Then, to choice of the best ammonium source, the model reaction was examined by various ammonium salts, such as HCO_2NH_4, NH_4NO_3, NH_4Cl, NH_4I, and NH_4HCO_3 (entries 14–18). As shown in Table 1, among various ammonium salts examined, NH_4OAc turned out to be the best choice, while others were less or none effective. Next , to optimize the time, we observed that decreasing the reaction time from 4 to 2 h reduces the yield of **3a** to 68 % (entry 19). Also, when the reaction time increased up to 6 h, no significant impact was seen in the yield (87 %) of desired product **3a** (entry 20). Then, to examine of reaction temperature, we tested the model reaction in both high and low temperatures of 120 °C, includes 140 and 100 °C. The isolated yields of **3a** were 65 and 52 %, respectively (entries 21 and 22). Finally, to evaluate of reaction medium, the effect of the several solvents, such as H_2O, DMSO, and $PhCH_3$, was investigated, that for H_2O and DMSO, **3a** was detected in 38 and 52 % yield (entries 23 and 24), respectively, and the reaction was ineffective by toluene as solvent (entry 25).

With the optimized reaction conditions in hand, the scope of the protocol was investigated for the reaction of a series of substituted benzonitriles **2a–2n**, isatoic anhydride (**1a**), and NH_4OAc, in the present of CuI, as the representative example (Table 2). First, the effect of the substituents at the *ortho*, *meta*, and *para*-position of benzonitriles was examined. Electron-donating groups (3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, and 4-NMe_2) on benzonitrile were well tolerated leading to the desired quinazolines **3b–3g** in yields of 70–82 % (entries 2–7). In addition, electron-withdrawing groups (2-Cl, 4-Cl, 4-F, 2-NO_2, and 3-NO_2) readily underwent reaction to afford the target products **3h–3l** in yields of 82–88 % (entries 8–12). Next, we used the 6-chloroisatoic anhydride **1b**, with benzonitrile (**2a**) and 4-methylbenzonitrile (**2c**) in optimal conditions that gave corresponding products **3m**, **3n** in good yields (entries 13 and 14). Finally, the reaction of the heterocyclic nitriles, furyl-2-nitrile (**2m**) and thienyl-2-nitrile (**2n**), with isatoic anhydride (**1a**) was used to afford the target products **3o**, **3p** in 77 and 81 % yield, respectively (entries 15 and 16).

The plausible mechanism for the formation of the quinazoline-4(3*H*)-ones **3** is suggested in Scheme 2. It is reasonable to assume that the anthranilamide (**4**) undergoes a decarboxylation, formed by nucleophilic addition of isatoic anhydride **1** with ammonia. Next, the prepared anthranilamide (**4**) is condensed by intermediate **5**, which is in situ prepared by coordination of nitrile **2** with CuI, to

Scheme 1

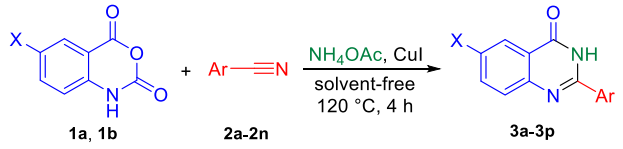
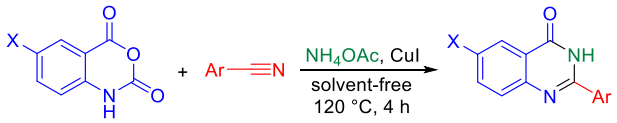


Table 1 Effect of different reaction conditions on synthesis of 2-phenylquinazolin-4(3*H*)-one



Entry	NH_4X (eq.)	Cat.	Temp./°C	Time/h	Yield[a]/%
1	NH_4OAc (1)	–	120	4	NR
2	NH_4OAc (1)	CuI	120	4	27
3	NH_4OAc (2)	CuI	120	4	46
4	NH_4OAc (3)	CuI	120	4	68
5	**NH_4OAc (4)**	CuI	**120**	**4**	**87**
6	NH_4OAc (5)	CuI	120	4	85
7[b]	NH_4OAc (4)	CuI	120	4	66
8[c]	NH_4OAc (4)	CuI	120	4	85
9	NH_4OAc (4)	$Cu(OAc)_2$	120	4	63
10	NH_4OAc (4)	CuO	120	4	75
11	NH_4OAc (4)	Cu_2O	120	4	55
12	NH_4OAc (4)	$CuCl_2$	120	4	68
13	NH_4OAc (4)	CuBr	120	4	82
14	HCO_2NH_4 (4)	CuI	120	4	64
15	NH_4NO_3 (4)	CuI	120	4	55
16	NH_4Cl (4)	CuI	120	4	NR
17	NH_4I (4)	CuI	120	4	NR
18	NH_4HCO_3 (4)	CuI	120	4	60
19	NH_4OAc (4)	CuI	120	2	68
20	NH_4OAc (4)	CuI	120	6	87
21	NH_4OAc (4)	CuI	140	4	65
22	NH_4OAc (4)	CuI	100	4	52
23[d]	NH_4OAc (4)	CuI	120	4	38
24[e]	NH_4OAc (4)	CuI	120	4	52
25[f]	NH_4OAc (4)	CuI	120	4	NR

Highlighted values represent the best reaction condition

Reaction conditions Isatoic anhydride (1 mmol), Benzonitrile (1 mmol)

NR no reaction

[a] Isolated yield

[b] CuI (5 mol%)

[c] CuI (15 mol%)

[d] H_2O (2 cm^3) as solvent employed

[e] DMSO (2 cm^3) as solvent employed

[f] Toluene (2 cm^3) as solvent employed

form the intermediate **6**. Then, intramolecular cyclization of intermediate **6**, followed by libration of ammonia, leads to the formation of the corresponding quinazoline-4(3*H*)-ones **3** (Scheme 2).

In summary, we have developed novel and efficient approach for the preparation of quinazoline-4(3*H*)-ones via a one-pot copper-catalyzed three-component condensation of isatoic anhydrides, aryl nitriles, and ammonium acetate under solvent-free conditions. The simplicity of the starting materials, one-pot procedure, as well as solvent-free conditions and good yields of the products are the main advantages of the reported method.

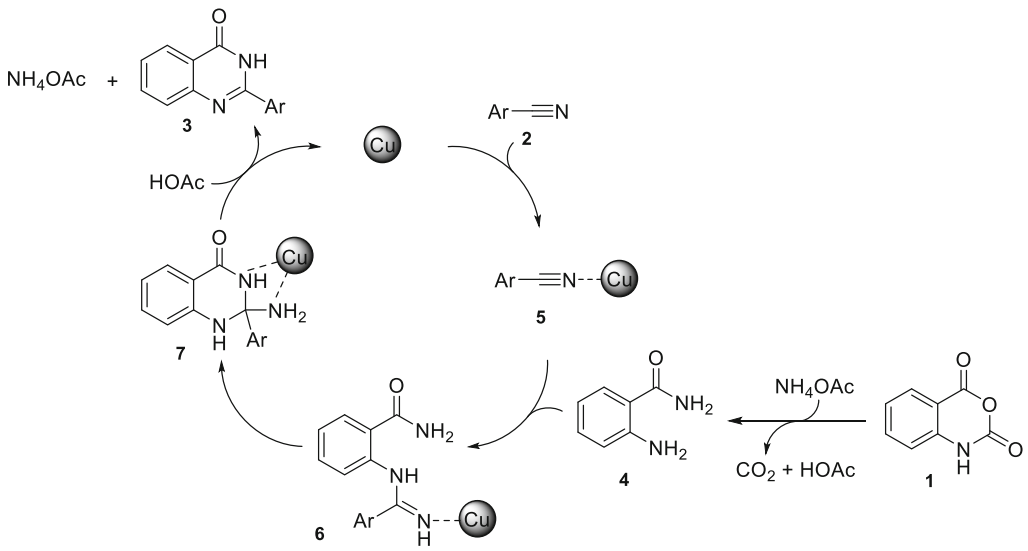
Table 2 The substrate scope of quinazolin-4(3*H*)-one derivatives

Entry	X	**1**	Ar	**2**	Yield[a]/ %	Product	M.p./°C	
							Observed	Reported
1	H	**1a**	Ph	**2a**	87	**3a**	233–235	234–235 [21]
2	H	**1a**	3-Me-Ph	**2b**	80	**3b**	204–206	210–212 [31]
3	H	**1a**	4-Me-Ph	**2c**	82	**3c**	260–262	261–263 [21]
4	H	**1a**	2-OMe-Ph	**2d**	70	**3d**	208–210	209–212 [29]
5	H	**1a**	3-OMe-Ph	**2e**	77	**3e**	206–208	209–210 [28]
6	H	**1a**	4-OMe-Ph	**2f**	75	**3f**	246–248	247–248 [21]
7	H	**1a**	4-NMe_2-Ph	**2g**	72	**3g**	236–238	236–238 [26]
8	H	**1a**	4-F-Ph	**2h**	83	**3h**	290–292	293–295 [27]
9	H	**1a**	2-Cl-Ph	**2i**	84	**3i**	195–197	196–197 [28]
10	H	**1a**	4-Cl-Ph	**2j**	88	**3j**	291–293	296–298 [21]
11	H	**1a**	2-NO_2-Ph	**2k**	82	**3k**	349–352	352–354 [20]
12	H	**1a**	3-NO_2-Ph	**2l**	83	**3l**	208–210	208–210 [26]
13	Cl	**1b**	Ph	**2a**	80	**3m**	288–290	295–296 [21]
14	Cl	**1b**	4-Me-Ph	**2c**	78	**3n**	296–297	300–302 [21]
15	H	**1a**	2-Furyl	**2m**	77	**3o**	214–216	210–212 [31]
16	H	**1a**	2-Thienyl	**2n**	81	**3p**	273–275	275–276 [21]

Reaction conditions Isatoic anhydride (1.0 mmol), Aryl nitrile (1.0 mmol), NH_4OAc (4.0 mmol), CuI (0.1 mmol), 120 °C, 4 h

[a] Isolated yield

Scheme 2



Experimental

All chemicals were purchased from Merck and Fluka companies. All yields refer to isolated products. IR spectra of the compounds were obtained on a Perkin Elmer GX FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500-MHz NMR spectrometer using tetramethylsilane (TMS) as internal standard. Melting points were determined in a capillary tube. The progress of reaction was followed with TLC using silica

gel SILG/UV 254 and 365 plates. All products are known compounds and were characterized by comparing the IR, ^{1}H and ^{13}C NMR spectroscopic data, and their melting points with the literature values.

Typical procedure for the preparation of compounds 3a–3p, exemplified with 3a

A mixture of isatoic anhydride (1.0 mmol), benzonitrile (1.0 mmol), NH_4OAc (4.0 mmol), and CuI (0.1 mmol) was heated for 4 h at 120 °C. After completion of the reaction as indicated by TLC monitoring, the reaction mixture was cooled to room temperature, and the residue was purified by column chromatography using *n*-hexane—EtOAc (4:1) as eluent. The solvent was removed, and the pure product **3a** was obtained as a white solid.

Acknowledgments This research was supported by the Research Council of Tehran University.

References

1. Lowe JA, Archer RL, Chapin DS, Cheng JB, Helweg D, Johnson JL, Koe BK, Lebel LA, Moore PF, Nielsen JA, Russo LL, Shirley JT (1991) J Med Chem 34:624
2. Kenichi O, Yoshihisa Y, Toyonari O, Toru I, Yoshio I (1985) J Med Chem 28:568
3. Kuarm BS, Reddy YT, Madhav JV, Crooks PA, Rajitha B (2011) Bioorg Med Chem Lett 21:524
4. Habib OM, Moawad EB, Girges MM, El-Shafei AM (1995) Boll Chim Farm 134:503
5. Lüth A, Löwe W (2008) Eur J Med Chem 43:1478
6. Cao SL, Feng YP, Jiang YY, Liu SY, Ding GY, Li RT (2005) Bioorg Med Chem Lett 15:1915
7. Malamas MS, Millen J (1991) J Med Chem 34:1492
8. Tereshima K, Shimamura H, Kawase A, Tanaka Y, Tanimura T, Kamisaki T, Ishizuka Y, Sato M (1995) Chem Pharm Bull 43:2021
9. Bedi PMS, Kumar V, Mahajan MP (2004) Bioorg Med Chem Lett 14:5211
10. Meyyanathan SN, Ramu M, Suresh B (2010) Med Chem Res 19:993
11. Aly MM, Mohamed YA, El-Bayouki KAM, Basyouni WM, Abbas SY (2010) Eur J Med Chem 45:3365
12. Wolfe JF, Rathman TL, Sleevi MC, Campbell JA, Greenwood TD (1990) J Med Chem 33:161
13. Li H, Huang R, Qiu D, Yang Z, Liu X, Ma J, Ma Z (1998) Prog Nat Sci 8:359
14. Chandrika PM, Yakaiah T, Narsaiah B, Sridhar V, Venugopal G, Rao JV, Kumar KP, Murthy USN, Rao ARR (2009) Indian J Chem 48:840
15. Mekala R, Akula R, Kamaraju RR, Bannoth CK, Regati S, Sarva J (2014) Synlett 25:821
16. Wei H, Li T, Zhou Y, Zhou L, Zeng Q (2013) Synthesis 45:3349
17. Cheng R, Guo T, Zhang-Negrerie D, Du Y, Zhao K (2013) Synthesis 45:2998
18. Romero AH, Salazar J, López SE (2013) Synthesis 45:2043
19. Hu BQ, Wang LX, Yang L, Xiang JF, Tang YL (2015) Eur J Org Chem 2015:4504
20. Adib M, Sheikhi E, Bijanzadeh HR (2012) Synlett 23:85
21. Xu W, Jin Y, Liu H, Jiang Y, Hua Y, Fu H (2011) Org Lett 13:1274
22. Zhou J, Fu L, Lv M, Liu J, Pei D, Ding K (2008) Synthesis 24:3974
23. Zheng Z, Alper H (2008) Org Lett 10:829
24. Liu JF, Lee J, Dalton AM, Bi G, Yu L, Baldino CM, McElory E, Brown M (2005) Tetrahedron Lett 46:1241
25. Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M (2005) Tetrahedron Lett 46:7051
26. Zhang J, Ren D, Ma Y, Wang W, Wu H (2014) Tetrahedron 74:5274
27. Jiang X, Tang T, Wang J, Chen Z, Zhu Y, Ji S (2014) J Org Chem 79:5082
28. Jianguang Z, Jie F (2011) J Org Chem 76:7730
29. Davoodnia A, Allameh S, Fakhari AR, Tavakoli-Hoseini N (2010) Chin Chem Lett 21:550
30. Tavakoli-Hoseini N, Davoodnia A (2011) Chin J Chem 29:1685
31. Rao KR, Mekala R, Raghunadh A, Meruva SB, Kumar SP, Kalita D, Laxminarayana E, Prasad B, Pal M (2015) RSC Adv 5:61575
32. Feng Y, Li Cheng YY, Wang L, Cui X (2015) J Org Chem 80:7099
33. Mhaske SB, Argade NP (2006) Tetrahedron 62:9787
34. Soheilizad M, Adib M, Sajjadifar S (2014) Monatsh Chem 145:1353
35. Soheilizad M, Adib M, Sajjadifar S (2014) J Chem Res 38:524
36. Adib M, Bayanati M, Soheilizad M, Ghazvini HJ, Tajbakhsh M, Amanlou M (2014) Synlett 25:2918
37. Adib M, Soheilizad M, Zhu LG, Wu J (2015) Synlett 26:177
38. Adib M, Soheilizad M, Rajai-daryasaraei S, Mirzaei P (2015) Synlett 26:1101