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Potassium hydroxide-promoted transition-metal-free synthesis of 4(3*H*)-quinazolinones

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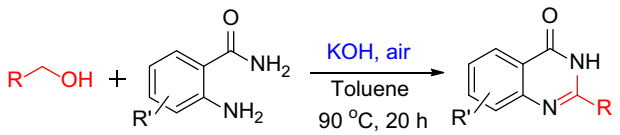
Abstract We have developed a KOH-promoted transition-metal-free synthesis of 2-substituted 4(3*H*)-quinazolinones from anthranilamides and benzyl alcohols or cinnamyl alcohol with air as oxidant. The protocol is simple, practical, and cost saving.

Graphical abstract



Keywords 4(3*H*)-Quinazolinones · Benzyl alcohols · Anthranilamides · Heterocycles · Potassium hydroxide

Introduction

4(3*H*)-Quinazolinones are important nitrogen-containing heterocycles, which are used as numerous synthetic drugs or drug candidates with a broad spectrum of bioactivities [1–3], such as anticancer agents [4], anti-inflammatory agents [5], antibacterial agents [6], anticonvulsant piriqualone [7]. Some synthetic quinazolinones, such as raltitrexed, ispinesib, tempostatin, halofuginone, have been sold in the pharmaceutical market or are currently in clinical trials for various cancer treatments. In addition, many natural products containing quinazolinone core structures, for example, luotonin alkaloids [8], rutaecarpine [9, 10], bouchardatine [11], have been reported as biologically important molecules [1–3, 12, 13]. Hence, to develop alternative synthetic methods of quinazolinones is of importance.

Among the synthesis of quinazolinones [14], the reaction of carboxylic acid derivatives with 2-aminobenzamide is the typical procedure [15–18]. Anthranilamide and (hetero)aryl aldehydes are common combination [19–24]. There are more two-component reaction systems [25–28] and three-component ones [29, 30].

More recently, the reaction of anthranilamides with benzyl alcohols come into the view of synthetic chemists [31–35]. Under hydrogen transfer conditions, Zhou adopted 2.5 mol% $[Cp^*IrCl_2]_2$ as a catalyst [31], and soon later Watson used $Ru(PPh_3)_3(CO)(H)_2$ (5 mol%) and xantphos (5 mol%) as a catalyst to fulfill the synthesis of quinazolinones [32]. Later Hikawa et al. reported a palladium-catalyzed synthetic protocol with $Pd(OAc)_2$ (5 mol%) and sodium (diphenylphosphino)benzene-3-sulfonate (10 mol%) as catalyst [33]. Very recently Wu adopted ZnI_2 as a catalyst and TBHP as a chemical oxidant to furnish this transformation [34]. The three methods above use 5 mol% (for Ir, Ru, and Pd) or 10 mol% (for ZnI_2) transition metals as catalysts, and some need additional chemicals as hydrogen acceptors or oxidant. Wei also reported an iodine-catalyzed synthesis of quinazolinones using DMSO as the oxidant, but this protocol has the shortcoming of emitting poisonous and foul-smelling dimethyl sulfide [35].

Most transition-metal catalysts are known to be expensive. Moreover, many transition metals are poisonous, and strict purification is demanded due to the strict requirements for pharmaceutical products [36, 37]. Thus recently

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transition-metal-free reactions attract the attention of more and more chemists [38–41].

As our ongoing research on synthesis of 4(3*H*)-quinazolinones [22, 23] and greener synthesis [42–44], we disclose in this paper KOH-promoted transition-metal-free oxidative domino synthesis of 2-substituted 4(3*H*)-quinazolinones with air oxidant (Scheme 1).

Results and discussion

To begin with, benzyl alcohol and anthranilamide were chosen as the model substrates (Table 1). In view of the reaction process involving oxidation of benzyl alcohol [31–35], the reaction was performed under air.

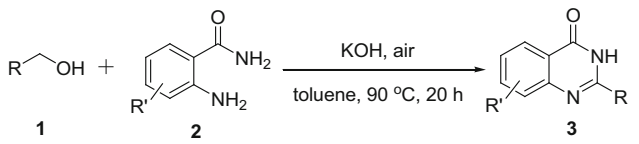
Aiming at exploring practical synthetic methods, we initially used less toxic and cheaper metal salts. After our extensive primary study, we discovered that combination of CuBr and KOH afforded 2-phenyl-4(3*H*)-quinazolinone with high yield (entry 1). Among the tested solvent, nonpolar solvent toluene gave the highest yield (entries 5 vs. 1–4). Without KOH, CuBr gave trace yield (entry 6). CuBr was a dispensable component, but KOH is absolutely necessary (entry 7). The reaction performed under argon hardly gave the desired product (entry 8), which means oxygen in the air is the real oxidant. Both decreasing the temperature and shortening time decreased the yield (entries 9 and 10). When KOH is replaced by NaOH, a lower yield was obtained (entry 11). K_2CO_3 gave nearly no product (entry 12). NaH with stronger basicity afforded excellent yields (entry 13), and Na, which will react with benzyl alcohol to form alkoxide, also gave a pretty good yield (entry 14). However, they are extremely moisture sensitive and much dangerous, thus KOH was used. The amount of KOH was also examined (entries 7 and 15–17). The same yield was obtained using highly pure KOH (99.999 % metals basis, except sodium; entries 18 vs. 17).

With the optimized conditions at hand, we next investigated the substrate scope (Table 2). A wide range of functional groups on the phenyl ring of benzyl alcohol were applicable (entries 2–14). Owing to steric hindrance, *ortho*-methylbenzyl alcohol gave lower yield than *para*- and *meta*-methylbenzyl alcohols (entries 4 vs. 2–3, 5–6). It seems that both strong electron-donating groups and strong electron-withdrawing groups disfavored the reaction (entries 1–6 vs. 7–8 and 9–12 vs. 13–14). Additionally, cinnamyl alcohol also was a good substrate (entry 15). Thus, our protocol is a good compensation for the synthesis of 2-styryl-4(3*H*)-quinazolinone [45, 46].

More anthranilamides were examined. Except for complicated heterocycle 3-aminobenzofuran-2-carboxamide (entry 21), all gave good or excellent yields (entries 16–20). Furthermore, the synthesis of 4(3*H*)-quinazolinones might be scaled up (entry 22).

In summary, 4(3*H*)-quinazolinones as a class of aromatic heterocycles have drawn great attention owing to their biological and pharmacological applications. KOH-promoted transition-metal-free oxidative domino reaction of anthranilamides and benzyl alcohols (or cinnamyl alcohol) using air as a green and cheap oxidant afforded 2-substituted 4(3*H*)-quinazolinones with good to excellent yields. In the scale-up procedure, toluene is recovered by vacuum distillation and the product is purified by recrystallization after workup. The protocol is practical and cost saving.

Scheme 1



Experimental

The chemicals were purchased from Aldrich, Adamas, Aladdin, Alfa Aesar, and Kelong chemical companies, and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using commercial silica gel plates (GF254). Purification of the synthesized compounds was carried out by flash column chromatography with silica gel (300–400 mesh). Melting points were determined on an X-4 melting-point apparatus with microscope. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or -400 spectrometer (300 or 400 MHz for ^{1}H NMR, and 75 or 101 MHz for ^{13}C NMR, respectively). Chemical shifts (δ) were reported in ppm referenced to an internal tetramethylsilane standard or the deuterated solvent DMSO-d_6 or $CDCl_3$. Coupling constants J were reported in Hertz (Hz). Combustion analyses are performed on a Euro EA-3000 elemental analyzer (Leeman Labs Inc.). Electrospray ionization mass spectra were recorded on an Agilent 1,200 series LC/MS DVL instrument. High-resolution mass spectra (HR-MS) were obtained with micrOTOF-Q II (Bruker Daltonics). All IR spectra were taken on a Bruker Tensor-27 infrared spectrometer with an OPUS workstation.

Typical procedure of synthesis of 4(3H)-quinazolinones

To an oven-dried 20 cm^3 test tube with a ground-in stopper equipped with a stir bar were added anthranilamide

Table 1 Optimization of conditions of reaction of benzyl alcohol (**1a**) and anthranilamide (**2a**)

Entry	Solvent	Catalyst	Base (mmol)	Yield/ %[a]
1	DMSO	CuBr	KOH (2)	85
2	DMF	CuBr	KOH (2)	60
3	DMA	CuBr	KOH (2)	76
4	1,4-Dioxane	CuBr	KOH (2)	89
5	Toluene	CuBr	KOH (2)	95
6	Toluene	CuBr	–	Trace
7	Toluene	–	KOH (2)	96
8[b]	Toluene	–	KOH (2)	Trace
9[c]	Toluene	–	KOH (2)	70
10[d]	Toluene	–	KOH (2)	94
11	Toluene	–	NaOH (2)	72
12	Toluene	–	K_2CO_3 (2)	Trace
13	Toluene	–	NaH (2)	95
14	Toluene	–	Na (2)	96
15	Toluene	–	KOH (1.0)	88
16	Toluene	–	KOH (1.2)	97
17[e]	Toluene	–	KOH (1.2)	97

Reaction conditions: benzyl alcohol (1.0 mmol), anthranilamide (1.0 mmol), with or without CuBr (0.05 mmol) as catalyst, base (2 mmol), 4 cm^3 solvent, under air, 90 °C, 20 h, unless otherwise noted

[a] Isolated yield

[b] Under argon

[c] 70 °C

[d] 17 h

[e] 99.999 % metals basis, except sodium. This is an Aladdin reagent

(1.0 mmol), benzyl alcohol (1.0 mmol), KOH (2.0 mmol), and 4 cm^3 toluene. The test tube was put in an oil bath pot preheated at 90 °C and the mixture was stirred for 20 h at 90 °C. After cooling to room temperature, the reaction mixture was added about 5 g silica gel and directly condensed on a rotator under vacuum. The resulting residual was transferred to a silica gel chromatography column and eluted with a solution of petroleum ether and ethyl acetate [4/1 (v/v)] to give a white solid 2-phenyl-4(3*H*)-quinazolinone. For some products (**3f**, **3g**, **3n**, and **3t**) only sparingly soluble in ethyl acetate, the reaction mixtures were condensed in vacuo on a rotary evaporator. The residuals were washed three times with water and once with ethyl acetate, and then dried in an infrared oven to give the desired products pure enough for NMR analysis.

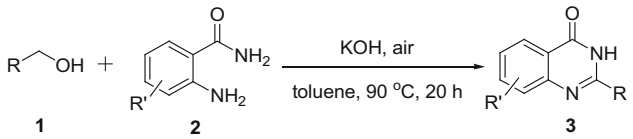
Scale-up procedure of synthesis of 2-phenyl-4(3H)-quinazolinone

To a 100 cm^3 round flask equipped with a stir bar were added 1.36 g anthranilamide (10 mmol), 1.08 g benzyl alcohol (10 mmol), 0.84 g KOH (15 mmol), and 30 cm^3 toluene. The flask was put in an oil bath pot preheated at 90 °C and the mixture was stirred for 20 h at 90 °C. Then toluene was removed by vacuum distillation. After quenching with aqueous NH_4Cl, the reaction mixture turned into solid. The solid crude product was filtered and recrystallized in ethanol to give pure 2-phenyl-4(3*H*)-quinazolinone with 82 % yield.

2-[4-(Methylthio)phenyl]quinazolin-4(3H)-one
(**3f**, $C_{15}H_{12}N_2OS$)
Yield: 91 %; white solid; m.p.: 262–263 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 12.4$ (s, 1H), 8.16–8.13 (m, 3H), 7.85–7.79 (m, 1H), 7.72 (d, $J = 1.8$ Hz, 1H), 7.52–7.50 (m, 1H), 7.48–7.38 (m, 2H), 2.55 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 162.2$, 151.8, 143.0, 134.5, 131.5, 128.6, 128.0, 127.3, 126.3, 125.8, 125.1, 120.8, 14.1 ppm; HR-MS (positive mode): *m/z* (calculated) for $C_{15}H_{13}N_2OS$ 269.0743, found 269.0855.

2-(3-Phenoxyphenyl)quinazolin-4(3H)-one
(**3 h**, $C_{20}H_{15}N_2O_2$)
Yield: 82 %; white solid; m.p.: 312–314 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 12.5$ (br, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.97–7.70 (m, 3H), 7.55–7.40 (m, 4H), 7.22–7.07 (m, 4H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 162.8$, 156.9, 156.5, 152.2, 148.7, 135.1, 134.5, 130.4, 130.2, 127.4, 126.6,

Table 2 Reactions of substituted benzyl alcohols **1** and anthranilamides **2**



1 2 3

Entry	*R*	*R′*	Product	Yield/%	M.p./ °C	Lit. m.p./ °C
1	Ph	H	**3a**	97	239–241	239–241 [22]
2	4-MePh	H	**3b**	97	240–241	240–241 [29]
3	3-MePh	H	**3c**	98	212–214	210–211 [27]
4	2-MePh	H	**3d**	84	214–216	212–215 [33]
5	4-(*i*-Pr)Ph	H	**3e**	89	220–222	211–213 [47]
6[a]	4-MeSPh	H	**3f**	91	262–263	–
7[a]	4-MeOPh	H	**3g**	80	250–252	255–257 [21]
8	3-PhOPh	H	**3h**	82	312–314	–
9	4-CF_3Ph	H	**3i**	84	309–311	310–312 [21]
10	3-CF_3Ph	H	**3j**	91	249–251	247–248 [48]
11	3-FPh	H	**3k**	95	276–278	279–280 [49]
12	2-FPh	H	**3l**	86	165–167	163–164 [50]
13	4-ClPh	H	**3m**	78	196–198	–
14[a]	4-NO_2Ph	H	**3n**	75	356–357	363 [51]
15	PhCH=CH	H	**3o**	90	243–245	238–240 [52]
16	Ph	5-CH_3	**3p**	98	237–239	238–239 [31]
17	Ph	4-Cl	**3q**	89	272–274	286–288 [53]
18	Ph	5-Cl	**3r**	98	282–284	282–284 [22]
19	4-MePh	6-F	**3s**	80	252–255	–
20	Ph	ATC[b]	**3t**	95	268–269	268–269 [54]
21[a]	3-MePh	ABFC[c]	**3u**	48	291–293	–
22[d]	Ph	H	**3a**	82	239–241	239–241 [22]

Reaction conditions: benzyl alcohol (1.0 mmol), anthranilamide (1.0 mmol), base (1.5 mmol), 4 cm^3 toluene, under air, 90 °C, 20 h, unless otherwise noted

[a] For 24 h

[b] ATC is 3-aminothiofuran-2-carboxamide

[c] ABFC is 3-aminobenzofuran-2-carboxamide, 0.2 eq

[d] (10 mmol), anthranilamide (10 mmol), base (15 mmol), 40 cm^3 toluene

125.9, 123.8, 122.9, 121.6, 121.1, 118.9, 117.9 ppm; HR-MS (positive mode): *m/z* (calculated) for $C_{20}H_{15}N_2O_2$ 315.1128, found 315.1150.

2-(4-Chlorophenyl)quinazolin-4(3H)-one
(**3 m**, $C_{14}H_9ClN_2O$)
Yield: 78 %; white solid; m.p.: 196–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 12.61$ (s, 1H), 8.18 (dd, $J = 14.3$, 8.3 Hz, 3H), 7.85 (t, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.63 (d, $J = 8.6$ Hz, 2H), 7.54 (t, $J = 7.5$ Hz, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 162.6$, 151.8, 148.9, 136.7, 135.1, 132.0 130.0, 129.1, 127.9, 127.2, 126.3, 121.4 ppm; ESI–MS (positive mode): $m/z = 257$ ($[M-H]^+$); IR (KBr): $\bar{\nu} = 2{,}922$, 1,671, 1,598, 1,476, 1,344, 1,280, 1,121, 1,093, 982, 760, 683 cm^{-1}.

5-Fluoro-2-(4-methylphenyl)quinazolin-4(3H)-one
(**3 s**, $C_{15}H_{11}FN_2O$)
Yield: 80 %; white solid, m.p.: 252–255 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 12.75$ (s, 1H), 8.35 (s, 2H), 7.98 (s, 1H), 7.74 (s, 3H), 7.44 (s, 1H), 3.53 (s, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 162.3$, 160.0, 159.7, 153.7, 151.3, 135.6 (d, $J = 10.6$ Hz), 132.6, 132.1, 129.1, 128.3, 124.0, 113.4, 113.2 ppm.

2-(3-Methylphenyl)benzofuro[3,2-d]pyrimidin-4(3H)-one (**3u**, $C_{17}H_{12}N_2O_2$)

Yield: 48 %; white solid; m.p.: 291–293 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 13.06$ (s, 1H), 8.13 (d, $J = 7.7$ Hz, 1H), 8.06–7.91 (m, 2H), 7.86 (d, $J = 8.3$ Hz, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.63–7.34 (m, 3H), 7.17–6.93 (m, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 156.3$, 154.5, 153.4, 138.1, 137.9, 131.9, 129.9, 129.1, 128.6, 128.5, 128.1, 127.7, 125.4, 125.1, 124.4, 122.4, 121.4, 113.0, 20.9 ppm; IR (KBr): $\bar{\nu} = 3{,}560$, 2,076, 1,637, 1,391, 1,085, 991, 546 cm^{-1}.

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