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# Copper-catalyzed synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones from benzyl-substituted anthranilamides

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**Abstract:** An efficient, practical approach to the copper-catalyzed synthesis of 2,3-disubstituted quinazolin-4(3*H*)-one derivatives is described. The preparation involves treatment of benzyl amines with benzyl anthranilamides in the presence of  $\text{Cu}(\text{OAc})_2$  and tetra-*n*-butylammonium bromide (TBAB).

**Keywords:** anthranilamide; copper acetate; quinazolin-4(3*H*)-one; TBAB.

## Introduction

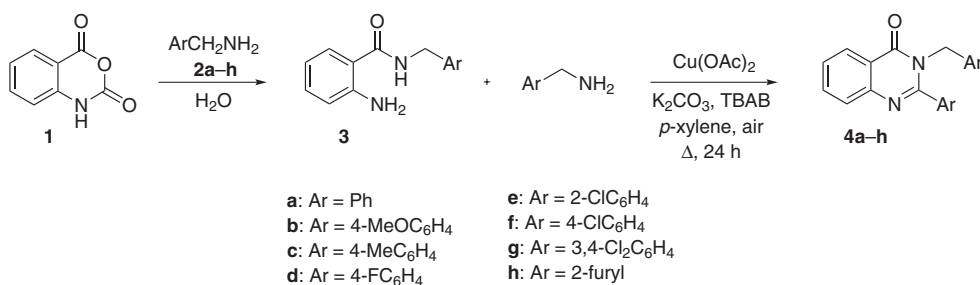
Nitrogen-containing heterocyclic compounds are privileged structures in medicinal chemistry [1–3]. Quinazolin-4(3*H*)-one is a significant pharmacophore among nitrogen-containing heterocyclic compounds, due to the various biological and pharmacological properties. Anticancer [4],

antimicrobial [5], anti-inflammatory [6], anticonvulsant [7], anti-ulcer [8], anti-bacterial [9] and aldose reductase inhibitory activity [10] are some of the biological properties of quinazolin-4(3*H*)-ones. Considering the remarkable biological activities of quinazolines [11], it is not surprising that many synthetic procedures have been reported, giving access to the libraries of this scaffold [12–20]. Transition-metal coupling reactions form important approaches to this class of compounds by utilizing various substrates, including palladium-catalyzed carbonylation of 2-aminobenzamide [21], palladium-catalyzed isocyanide insertion/cyclization sequence between 2-aminobenzamides and aryl halides [22], C-H bond carboxamidation of *N*-aryl-amidines catalyzed by palladium acetate [23] and coupling reaction between 2-bromobenzoic acid and amidines catalyzed by CuI [24]. In our previous report, oxidative synthesis of 2-substituted quinazolin-4(3*H*)-ones starting from benzyl-substituted anthranilamides was described [25]. Surprisingly, it was found that 2,3-disubstituted quinazolin-4(3*H*)-ones are formed as the major products from the same substrates and benzylamines in the reaction conducted under similar conditions. This work is a continuation of our efforts directed toward the development of new heterocyclic chemistry [26–31].

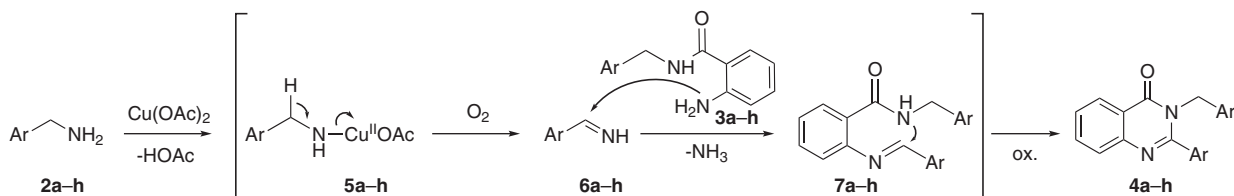
## Results and discussion

A new pathway for the preparation of 2,3-disubstituted quinazolin-4(3*H*)-ones by the reaction of *N*-benzylanthranilamides **3a–h** with benzylamines is shown in Scheme 1. The substrates **3a–h** are easily prepared by treatment of isatoic anhydride (**1**) with benzylamines **2a–h** in aqueous media. In order to optimize the reaction condition, the synthesis of 3-benzyl-2-phenylquinazolin-4(3*H*)-one (**4a**) was chosen as a model reaction. First, the effects of tetra-*n*-butylammonium bromide (TBAB) and  $\text{Cu}(\text{OAc})_2$  were evaluated in this reaction in the presence of  $\text{K}_2\text{CO}_3$  in *p*-xylene. The best yield of the product was obtained in the presence of 20 mol% of TBAB and 5 mol% of  $\text{Cu}(\text{OAc})_2$ . Different solvents including toluene, *N,N*-dimethylformamide (DMF)

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**Scheme 1** Synthesis of compounds **4a–h** from *N*-benzylanthranilamides.



**Scheme 2** Suggested mechanism for the synthesis of quinazolin-4(3*H*)-ones **4**.

and dimethyl sulfoxide (DMSO) were also investigated. However, these changes did not enhance the yield of the desired product as compared with the use of *p*-xylene. The important role of air in this reaction was demonstrated by performing the reaction under inert atmosphere, which led to trace amounts of the desired product only. As shown in Scheme 1, the reactions of aromatic benzylamines containing electron-donating groups, such as Me and OMe, or electron-withdrawing groups, such as F and Cl, furnish the corresponding products **4a–h** in 61–77% yields. An attempted synthesis with aliphatic amines was not successful, however. The structures of all synthesized products were confirmed by analytical and spectral data including Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (<sup>1</sup>H NMR), <sup>13</sup>C NMR and mass spectrometry (MS). For example, in the <sup>1</sup>H NMR spectra the CH<sub>2</sub> benzylic group for sterically unhindered molecules appears as a singlet. By contrast, the restricted rotation in **4e** gives rise to the appearance of benzylic protons as an AB system with two doublets at δ 4.90 and 5.51.

As suggested in Scheme 2, the mechanism may involve coordination of Cu(II) with benzylamine followed by oxidation of the resultant complex **5** to benzylamine **6**. A subsequent addition reaction of **3** with **6** may generate intermediate product **7** which is the final precursor to **4** [32–34].

## Conclusions

A straightforward, copper-catalyzed approach to the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones from benzyl anthranilamides is described. The simplicity of the

procedure, ready availability of the starting materials and good yields are the main advantages of this method.

## Experimental

All commercially available chemicals and reagents were purchased from Merck or Fluka and were used without further purification. Melting points were measured with a Koffler hot stage apparatus and are uncorrected. <sup>1</sup>H NMR (500 MHz) and <sup>13</sup>C NMR (125 MHz) spectra were recorded on a Bruker FT-500 spectrometer in DMSO-*d*<sub>6</sub>, using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu 470 spectrophotometer in KBr disks. electron ionization (EI) mass spectra were obtained using an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed using an Elemental Analysen system.

### General procedure for the synthesis of *N*-benzylanthranilamides **3a–h**

A mixture of isatoic anhydride **1** (1 mmol) and benzylamine **2a–h** (1 mmol) in H<sub>2</sub>O (10 mL) was stirred at room temperature. Upon completion of the reaction, as monitored by thin-layer chromatography (TLC), the resulting precipitate was filtered, washed with cold water, dried and crystallized from ethanol to afford the desired compound **3a–h**.

### General procedure for the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones **4a–h**

A mixture of *N*-benzylanthranilamide **3a–h** (1 mmol), Cu(OAc)<sub>2</sub> (5 mol%), K<sub>2</sub>CO<sub>3</sub> (1 mmol) and TBAB (20 mol%) in *p*-xylene (10 mL) was stirred for 24 h under reflux. Upon completion of the reaction, as

indicated by TLC analysis, the mixture was cooled and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (4:1) to afford pure product **4a–h**.

**3-Benzyl-2-phenylquinazolin-4(3H)-one (4a)** This compound was obtained as a white solid; yield 65%; mp 150–152°C (lit mp 152–153°C, [19, 35, 36]); IR: 2949, 1682, 1567, 1271 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.51–7.40 (m, 5H), 7.24–7.18 (m, 3H), 6.92–6.90 (m, 2H), 5.18 (s, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 161.9, 156.6, 147.4, 137.2, 135.6, 135.2, 130.2, 128.9, 128.7, 128.4, 127.8, 127.7, 127.5, 126.9, 126.7, 120.8, 48.7. Anal. Calcd for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.56; H, 5.35; N, 9.14.

**3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one (4b)** This compound was obtained as a white solid; yield 77%; mp 158–160°C; IR: 3061, 2952, 1677, 1577, 1266 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.36 (d, *J* = 7.3 Hz, 1H), 7.81–7.76 (m, 2H), 7.54–7.51 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.26 (s, 2H), 3.87 (s, OCH<sub>3</sub>), 3.77 (s, OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 162.4, 161.0, 158.9, 156.5, 134.6, 132.3, 130.6, 129.8, 129.6, 129.2, 128.6, 128.3, 127.7, 127.1, 120.6, 117.4, 55.4, 55.2, 48.4; MS: *m/z* (%) 372 (M<sup>+</sup>, 31), 341 (19), 265 (43), 145 (100), 121 (59), 77 (25). Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.89; H, 5.67; N, 7.76.

**3-(4-Methylbenzyl)-2-(*p*-tolyl)quinazolin-4(3H)-one (4c)** This compound was obtained as a white solid; yield 72%; mp 144–146°C; IR: 3053, 2948, 1566, 1273 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.36 (d, *J* = 7.9 Hz, 1H), 7.78–7.77 (m, 2H), 7.53–7.50 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 5.25 (s, CH<sub>2</sub>), 2.42 (s, CH<sub>3</sub>), 2.29 (s, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 162.5, 156.7, 147.2, 140.1, 137.1, 134.5, 133.6, 132.4, 129.2, 129.2, 128.0, 127.4, 127.1, 127.0, 126.9, 120.8, 48.7, 21.4, 21.0; MS: *m/z* (%) 340 (M<sup>+</sup>, 22), 325 (31), 311 (12), 235 (71), 145 (100), 91 (19), 77 (34). Anal. Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.00; H, 5.74; N, 8.41.

**3-(4-Fluorobenzyl)-2-(4-fluorophenyl)quinazolin-4(3H)-one (4d)** This compound was obtained as a white solid; yield 61%; mp 171–173°C; IR: 3064, 2966, 1667, 1572, 1256 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.33 (d, *J* = 8.5 Hz, 1H), 7.73–7.71 (m, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.35–7.32 (m, 3H), 7.14–7.11 (m, 3H), 6.89–6.80 (m, 3H), 5.31 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 164.6, 162.6 (d, *J*<sub>C-F</sub> = 175 Hz), 161.2 (d, *J*<sub>C-F</sub> = 124 Hz), 155.4, 145.5, 135.1, 133.2, 131.9, 131.1, 130.2 (d, *J*<sub>C-F</sub> = 7.8 Hz), 129.3, 128.8 (d, *J*<sub>C-F</sub> = 7.8 Hz), 126.5, 121.8, 115.8 (d, *J*<sub>C-F</sub> = 21.4 Hz), 115.5 (d, *J*<sub>C-F</sub> = 21.7 Hz), 48.2; MS: *m/z* (%) 348 (M<sup>+</sup>, 44), 239 (73), 144 (100), 109 (62), 95 (41). Anal. Calcd for C<sub>21</sub>H<sub>14</sub>F<sub>2</sub>N<sub>2</sub>O: C, 72.41; H, 4.05; N, 8.04. Found: C, 72.60; H, 4.23; N, 7.86.

**3-(2-Chlorobenzyl)-2-(2-chlorophenyl)quinazolin-4(3H)-one (4e)** This compound was obtained as a white solid; yield 70%; mp 176–178°C; IR: 3063, 2962, 1673, 1572, 1277 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.5 Hz, 1H), 7.36–7.30 (m, 3H), 7.24–7.20 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 16.5 Hz, 1H), 4.90 (d, *J* = 16.5 Hz, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 161.0, 152.8, 146.8, 134.8, 133.3, 132.9, 131.4, 131.3, 131.1, 129.8, 129.3, 128.9, 128.7, 128.6, 127.6, 127.4, 127.2, 127.1, 126.5, 120.4, 45.0; MS: *m/z* (%) 383 (M<sup>+</sup> + 2, 10), 381 (M<sup>+</sup>, 33), 269 (28), 145 (100), 125 (29), 111 (58), 76 (44). Anal. Calcd for C<sub>21</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 66.16; H, 3.70; N, 7.35. Found: C, 66.00; H, 3.49; N, 7.54.

**3-(4-Chlorobenzyl)-2-(4-chlorophenyl)quinazolin-4(3H)-one (4f)** This compound was obtained as a white solid; yield 72%; mp 164–166°C; IR: 3054, 2962, 1666, 1559, 1258 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.16 (s, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 161.3, 154.9, 146.8, 135.5, 134.7, 134.6, 133.7, 131.8, 129.8, 128.3, 128.2, 127.3 (2C), 126.4 (2C), 120.3, 47.6; MS: *m/z* (%) 383 (M<sup>+</sup> + 2, 15), 381 (M<sup>+</sup>, 40), 345 (55), 269 (61), 144 (100), 124 (44), 76 (29). Anal. Calcd for C<sub>21</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 66.16; H, 3.70; N, 7.35. Found: C, 66.38; H, 3.89; N, 7.19.

**3-(3,4-Dichlorobenzyl)-2-(3,4-dichlorophenyl)quinazolin-4(3H)-one (4g)** This compound was obtained as a white solid; yield 63%; mp 160–162°C; IR: 3064, 2968, 1677, 1564, 1256 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.0 Hz, 1H), 7.73–7.70 (m, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.24 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.12 (s, 2H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 161.30, 153.49, 146.67, 137.61, 135.14, 134.69, 132.68, 131.13, 131.01, 130.52, 130.45, 130.17, 129.78, 128.88, 128.08, 127.40, 127.30, 126.76, 126.34, 120.47, 47.33; MS: *m/z* (%) 454 (M<sup>+</sup> + 4, 11), 452 (M<sup>+</sup> + 2, 16), 450 (M<sup>+</sup>, 43), 303 (41), 159 (51), 144 (100), 77 (34). Anal. Calcd for C<sub>21</sub>H<sub>12</sub>Cl<sub>4</sub>N<sub>2</sub>O: C, 56.03; H, 2.69; N, 6.22. Found: C, 55.86; H, 2.85; N, 6.44.

**2-(Furan-2-yl)-3-(furan-2-ylmethyl)quinazolin-4(3H)-one (4h)** This compound was obtained as a white solid; yield 65%; mp 173–175°C; IR: 3057, 2946, 1664, 1571, 1263 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.33 (d, *J* = 8.1 Hz, 1H), 7.78–7.74 (m, 1H), 7.66 (d, *J* = 1.3 Hz, 1H), 7.51 (dd, *J* = 5.4, 2.8 Hz, 1H), 7.49 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.29 (d, *J* = 1.3 Hz, 1H), 7.14 (d, *J* = 3.4 Hz, 1H), 6.60 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.25 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 5.26 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 162.04, 149.60, 147.32, 147.20, 145.83, 144.43, 142.26, 134.55, 127.57, 127.25, 127.12, 120.65, 115.63, 111.99, 110.44, 108.44, 41.13; MS: *m/z* (%) 292 (M<sup>+</sup>, 29), 225 (50), 145 (100), 82 (47), 67 (33). Anal. Calcd for C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.98; H, 4.09; N, 9.66.

## Supplementary information (online only)

Characterization of compounds **3a–h**.

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