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Synthesis of quinazolin-4(3*H*)-ones *via* the reaction of isatoic anhydride with benzyl azides in the presence of potassium *tert*-butoxide in DMSO

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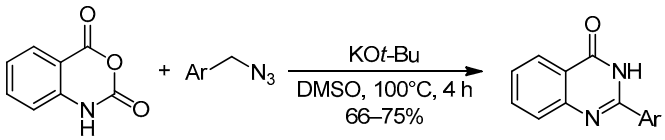


In this paper, a novel method is described for the synthesis of quinazolin-4(3*H*)-one derivatives *via* the reaction of isatoic anhydride with benzyl azides in the presence of potassium *tert*-butoxide in DMSO. The reaction is completed after 4 h at 100°C to produce the title products in good yields.

Keywords: benzyl azides, isatoic anhydride, potassium *tert*-butoxide, quinazolin-4(3*H*)-ones.

Quinazolin-4(3*H*)-ones are significant group of heterocyclic compounds possessing a broad range of therapeutic and pharmacological activities,[1] such as anticonvulsant,[2] anticancer,[3] hypolipidemic,[4] antiulcer,[5] anti-inflammatory,[6] antimicrobial, and cytotoxic activities.[7] In addition, some quinazolinone derivatives have been reported as active antimycobacterial agents against the strains of *M. tuberculosis*, *M. avium*, *M. fortuitum*, *M. kansasii*, and *M. intracellulare*.[8] The bioactive natural products febrifugine and isofebrifugine are examples of clinically important quinazolinone derivatives with antimalarial activity.[9–11]

Due to this wide range of activities, many synthetic routes have been reported for the preparation of quinazolin-4(3*H*)-ones,[12] such as reaction of nitriles with lithiated anthranilamides,[13] microwave-assisted condensation of anthranilic acids, carboxylic acids, and amines,[14] carboxylation of *ortho* C–H bonds in anilides leading to *N*-acylanthranilic acids and then treatment with anilines in the presence of PCl_3,[15] condensation of imidates with anthranilic acids,[16] Pd-catalyzed oxidative insertion reaction of isocyanide with anthranilamide,[17] condensation of aldehydes and anthranilamide or its derivatives in the presence of $CuCl_2$,[18] condensation of aldehydes and anthranilamide in the presence of Cu–β-cyclodextrin-modified nanoparticles,[19] condensation of *o*-bromobenzoic esters with isothiocyanates and azides in the presence of CuBr,[20] condensation of benzylacetamide and anthranilamide in the presence of a Cu(II)–polyethyleneimine-modified graphene oxide,[21] condensation of aldehydes and anthranilamide or isatoic anhydride in the presence of a nanoparticle-supported Pd catalyst,[22] amine-induced thermal rearrangement of iminobenzoxazines,[23] phosphine-catalyzed intramolecular aza-Wittig reaction,[24] oxidative reaction between benzyl halides, isatoic anhydride, and primary amines,[25] Pd-catalyzed carbonylative cyclization of *o*-bromoanilines, trimethyl orthoformate, and amines,[26] and CuI-catalyzed reaction between anthranilamide, terminal alkynes, and azides.[27] Isatoic anhydride is an interesting starting material for the synthesis of quinazolinone and is widely used for such synthesis.[28]

However, some of the starting materials of previously listed routes have to be synthesized and purified first,

therefore, these methods are time-consuming. The multistep procedures have also notable drawbacks, such as long reaction times, harsh reaction conditions, difficult workup, and low yields of the products. In addition, some of these protocols proceeded using expensive and environmentally toxic catalysts or reagents. Therefore, the development of simple and efficient methods for the synthesis of quinazolin-4(3*H*)-ones is still desirable.

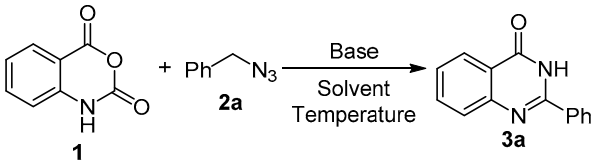
Herein, we wish to report an efficient synthesis of quinazolin-4(3*H*)-one derivatives *via* the reaction of isatoic anhydride (**1**) with benzyl azides in basic medium. Therefore, a model reaction using benzyl azide (**2a**), was investigated under various reaction conditions.

At first, the reaction was studied in the presence of KO*t*-Bu in various solvents. DMSO was found to be the best solvent (Table 1, entries 3, 4). The mole ratio of benzyl azide (**2a**) to isatoic anhydride (**1**) was 1:1 in all experiments, and the reactions were performed in 4 ml of solvent. Then a variety of bases such as K_2CO_3, Cs_2CO_3, and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) were studied for this reaction in DMSO. However, the reaction did not proceed in the presence of these bases (Table 1, entries 5–7). It was found that the best yield of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**3a**) was obtained at 100°C in the presence of KO*t*-Bu in DMSO after 4 h, when 1 equiv of KO*t*-Bu was applied (Table 1, entry 3). Therefore these conditions were selected as optimal.

To study the generality of the new protocol, we examined the reaction between isatoic anhydride (**1**) and various benzyl azides **2a**–**h** under optimal conditions to produce the corresponding quinazolin-4(3*H*)-one derivatives **3a**–**h** (Scheme 1). All the reactions were complete within 4 h. ^{1}H and ^{13}C NMR analysis of the reaction mixtures clearly indicated formation of quinazolin-4(3*H*)-one derivatives **3a**–**h** in good yields.

Formation of quinazolin-4(3*H*)-one derivatives **3** could be rationalized *via* a plausible mechanism provided in Scheme 2. Treatment of benzyl azide **2** with KO*t*-Bu leads to the generation of anionic intermediates **4** and **5** and

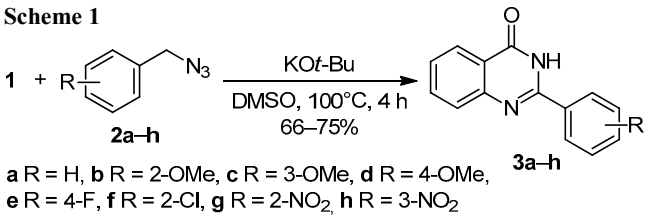
Table 1. Optimization of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**3a**) synthesis*



Entry	Base (equiv)	Solvent	Temperature, °C	Yield, %
1	KO*t*-Bu (1)	THF	Reflux	15
2	KO*t*-Bu (1)	DMF	100	51
3	KO*t*-Bu (1)	DMSO	100	75
4	KO*t*-Bu (2)	DMSO	100	70
5	K_2CO_3 (2)	DMSO	100	0
6	Cs_2CO_3 (2)	DMSO	100	0
7	DBU (2)	DMSO	100	0

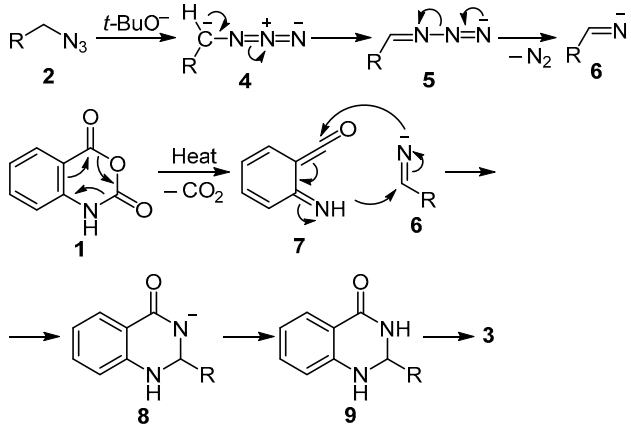
* Isatoic anhydride (**1**) (1 mmol), BnN_3 (**2a**) (1 mmol), solvent (4.0 ml), reaction time 4 h.

Scheme 1



removal of a nitrogen molecule to form anion **6**. Concurrently, isatoic anhydride (**1**) forms decarboxylated intermediate **7** *via* heating of the reaction mixture. The [4+2] addition of intermediates **6** and **7** leads to formation of compound **8**. This intermediate is protonated to give 2,3-dihydroquinazolin-4(1*H*)-one **9** which could undergo oxidation under the reaction conditions to produce the desired quinazolin-4(3*H*)-one **3**.

Scheme 2



In conclusion, we have developed an efficient protocol for the synthesis of quinazolin-4(3*H*)-one derivatives. The desired products were obtained in good yields. Use of commercially available materials and simple procedure are advantages of our protocol.

Experimental

IR spectra were obtained on a Bruker Tensor 27 spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 500 series NMR spectrometer (500 and 125 MHz, respectively) in DMSO-d_6, using TMS as internal standard. Elemental analysis was performed on a Thermo Finnigan FlashEA 1112 series instrument. Melting points were determined in a capillary tube on a Buchi apparatus. The progress of reaction was followed by TLC (eluent hexane–EtOAc, 4:1) using Merck 60 F_{254} silica gel plates.

All chemicals were purchased from Merck and Fluka companies. All products are known compounds and were identified by comparing the IR, ^{1}H and ^{13}C NMR spectroscopic data, as well as melting points with the literature data.

Synthesis of quinazolin-4(3*H*)-ones 3a–h (General method). A mixture of benzyl azide **2a**–**h** (1 mmol), isatoic anhydride (**1**) (0.163 g, 1 mmol), and KO*t*-Bu (1 mmol) in DMSO (4 ml) was stirred at 100°C for 4 h. Upon

completion, the reaction mixture was cooled to room temperature and H_2O (4 ml) was added. The stirring was continued for 1 h at ambient temperature. Next, the organic phase was extracted with CH_2Cl_2 (2×4 ml), and the combined organic layers were dried over Mg_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography using *n*-hexane–EtOAc, 3:1, as eluent.

2-Phenylquinazolin-4(3*H*)-one (3a). Yield 0.156 g (75%). White solid. Mp 234–236°C (mp 230–232°C[30]). IR spectrum, ν, cm^{-1}: 3315 (NH), 1661 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.51–7.61 (4H, m, H Ar); 7.75 (1H, d, *J* = 8.5, H Ar); 7.84 (1H, t, *J* = 8.5, H Ar); 8.16 (1H, d, *J* = 8.5, H Ar); 8.20 (2H, d, *J* = 7.5, H Ar); 12.50 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 120.7; 125.9; 126.5; 127.6; 127.8; 128.4; 130.9; 132.8; 134.2; 148.8; 152.0; 161.9. Found, %: C 75.69; H 4.49; N 12.67. $C_{14}H_{10}N_2O$. Calculated, %: C 75.66; H 4.54; N 12.60.

2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (3b). Yield 0.181 g (72%). White solid. Mp 202–204°C (mp 200–202°C[30]). IR spectrum, ν, cm^{-1}: 3324 (NH), 1661 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.88 (3H, s, OCH_3); 7.08 (1H, t, *J* = 7.5, H Ar); 7.19 (1H, d, *J* = 8.0, H Ar); 7.50–7.55 (2H, m, H Ar); 7.70 (1H, d, *J* = 7.5, H Ar); 7.49 (1H, d, *J* = 7.5, H Ar); 7.82 (1H, t, *J* = 7.5, H Ar); 8.16 (1H, d, *J* = 7.5, H Ar); 12.00 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.7; 112.0; 120.1; 121.1; 122.4; 125.8; 126.2; 127.4; 130.1; 131.9; 134.0; 149.0; 152.3; 156.9; 160.8. Found, %: C 71.45; H 4.83; N 11.06. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.79; N 11.10.

2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (3c). Yield 0.184 g (73%). White solid. Mp 180–182°C (mp 180–182°C[30]). IR spectrum, ν, cm^{-1}: 3324 (NH), 1667 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.87 (3H, s, OCH_3); 7.14 (1H, d, *J* = 7.5, H Ar); 7.45 (1H, t, *J* = 8.0, H Ar); 7.52 (1H, t, *J* = 8.0, H Ar); 7.73–7.85 (4H, m, H Ar); 8.16 (1H, t, *J* = 8.5, H Ar); 12.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.2; 112.6; 117.2; 119.8; 121.1; 125.6; 126.2; 127.3; 129.7; 134.0; 134.5; 148.4; 152.0; 159.6; 162.4. Found, %: C 71.40; H 4.82; N 11.14. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.79; N 11.10.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3d). Yield 0.184 g (73%). White solid. Mp 247–248°C (mp 244–245°C (DMF–H_2O)[29]). IR spectrum, ν, cm^{-1}: 3313 (NH), 1667 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, CH_3); 7.08 (2H, d, *J* = 8.0, H Ar); 7.48 (1H, t, *J* = 7.0, H Ar); 7.70 (1H, d, *J* = 7.0, H Ar); 7.80 (1H, t, *J* = 7.0, H Ar); 8.14 (1H, d, *J* = 7.0, H Ar); 8.20 (2H, d, *J* = 8.0, H Ar); 12.33 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.4; 114.0; 120.4; 124.6; 125.8; 126.1; 126.9; 129.4; 134.2; 148.7; 152.0; 161.6; 162.3. Found, %: C 71.45; H 4.83; N 11.07. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.79; N 11.10.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3e). Yield 0.158 g (66%). Yellow solid. Mp 289–291°C (mp 284–286°C[30]). IR spectrum, ν, cm^{-1}: 3315 (NH), 1666 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.38 (2H, t, *J* = 8.5, H Ar); 7.52 (1H, t, *J* = 7.0, H Ar); 7.73 (1H, d, *J* = 7.0, H Ar); 7.83 (1H, t, *J* = 7.0, H Ar); 8.15 (1H, d, *J* = 7.0, H Ar); 8.26 (2H, dd, *J* = 8.5, *J* = 5.5, H Ar); 12.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 115.4 (d, $^2J_{CF}$ = 22.6); 120.8; 125.7; 126.4; 127.3; 129.2; 130.3 (d, $^3J_{CF}$ = 8.8); 134.4; 148.5; 151.3; 162.5 (d, $^1J_{CF}$ = 104.3); 164.9. Found, %: C 70.02; H 3.84; N 11.71. $C_{14}H_9FN_2O$. Calculated, %: C 69.99; H 3.78; N 11.66.

2-(2-Chlorophenyl)quinazolin-4(3*H*)-one (3f). Yield 0.179 g (70%). White solid. Mp 196–197°C (mp 200–202°C[31]). IR spectrum, ν, cm^{-1}: 3317 (NH), 1656 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.50 (1H, t, *J* = 8.5, H Ar); 7.62–7.75 (3H, m, H Ar); 7.67 (1H, d, *J* = 8.0, H Ar); 7.71 (1H, d, *J* = 8.5, H Ar); 7.85 (1H, t, *J* = 8.5, H Ar); 8.19 (1H, d, *J* = 8.5, H Ar); 12.58 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 121.2; 125.6 (2C); 127.0; 126.9; 127.3; 129.7; 130.5; 131.6; 133.8; 134.2; 148.4; 151.9; 161.2. Found, %: C 65.59; H 3.49; N 10.97. $C_{14}H_9ClN_2O$. Calculated, %: C 65.51; H 3.53; N 10.91.

2-(2-Nitrophenyl)quinazolin-4(3*H*)-one (3g). Yield 0.182 g (68%). Yellow solid. Mp 221–323°C (mp 224–226°C (EtOAc)[29]). IR spectrum, ν, cm^{-1}: 3317 (NH), 1655 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.57 (1H, t, *J* = 8.0, H Ar); 7.66 (1H, d, *J* = 8.0, H Ar); 7.81–7.93 (4H, m, H Ar); 8.18–8.22 (2H, m, H Ar); 12.79 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 121.1; 124.4; 125.8; 127.0; 127.2; 129.1; 131.3; 131.4; 133.8; 134.5; 147.4; 148.4; 151.6; 161.4. Found, %: C 63.03; H 3.43; N 15.75. $C_{14}H_9N_3O_3$. Calculated, %: C 62.92; H 3.39; N 15.72.

2-(3-Nitrophenyl)quinazolin-4(3*H*)-one (3h). Yield 0.187 g (70%). Yellow solid. Mp 350–352°C (mp >300°C (EtOAc)[29]). IR spectrum, ν, cm^{-1}: 3317 (NH), 1658 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.57 (1H, t, *J* = 8.0, H Ar); 7.79–7.86 (3H, m, H Ar); 8.17 (1H, d, *J* = 7.5, H Ar); 8.41 (1H, d, *J* = 7.5, H Ar); 8.61 (1H, d, *J* = 7.5, H Ar); 9.02 (1H, s, H Ar); 12.82 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 122.6; 125.6; 125.8; 127.0; 127.5; 130.2; 133.9 (2C); 134.3; 134.6; 147.9; 149.2; 154.9; 162.1. Found, %: C 62.85; H 3.29; N 15.69. $C_{14}H_9N_3O_3$. Calculated, %: C 62.92; H 3.39; N 15.72.

Supplementary information file containing ^1H and ^{13}C NMR spectra of compounds **3a**–**h** is available at the journal website at http://link.springer.com/journal/10593.

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