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SODIUM SULFIDE-PROMOTED REACTION OF 2-AMINOBENZAMIDE AND BENZYL ALCOHOLS WITH ELEMENTAL SULFUR: A NOVEL APPROACH WITH 2-ARYL-QUINAZOLIN-4(*3H*)

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Abstract. A simple metal- and solvent-free method for the synthesis of 2-aryl-4(*3H*)-quinazolinone derivatives from 2-aminobenzamide and benzyl alcohols in the presence of S_8/DMSO as an oxidizing agent and promoted by $Na_2S.5H_2O$ has been reported. Five 2-aryl-4(*3H*)-quinazolinone derivatives were synthesized with yields from 23% to 86%.

Keywords: elemental sulfur, 2-aryl-4(*3H*)-quinazolinone, 2-aminobenzamide, benzyl alcohols, oxidative condensation.

1. Introduction

Quinazolinone-4(*3H*)-one derivatives are an important class of fused heterocyclic compounds having wide occurrence in natural products and synthetic drugs [1]. Because of their important applications, many synthetic efforts have been made to construct quinazolinone-4(*3H*)-one derivatives starting from a variety of substrates, among which, 2-aminobenzamide is probably the most typical substance. Recently, the direct oxidative cyclization of primary alcohols with 2-aminobenzamide to form nitrogen heterocyclic rings has attracted much attention. Many oxidation coupling methods have been reported using metal catalysts (Scheme 1, eq a) including Ir [2], Pd [3, 4], Zn [5], and Fe [6]. In addition, Yunyang Wei *et al.* [7] used a convenient and efficient two-step one-pot oxidation system catalyzed by iodine to synthesize quinazolinones from the cyclization of primary alcohols and 2-aminobenzamide using DMSO as the oxidizing agent (Scheme 1, eq b).

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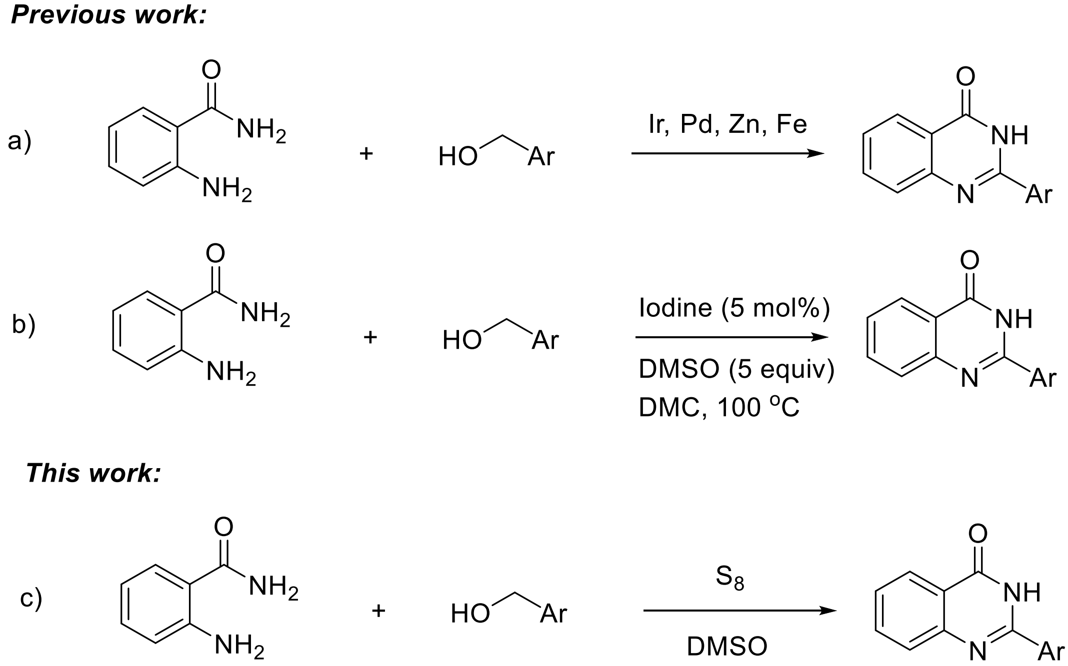


Scheme 1. Some approaches for the synthesis of 2-aryl-quinazolin-4(3H)-one derivatives

The use of elemental sulfur as a coupling redox promoter is a promising strategy in organic synthesis that replaces many transition metals. In particular, the catalytic role of elemental sulfur in DMSO promoting the oxidative coupling of C(sp^3)-H bonds is very attractive allowing the synthesis of convenient nitrogen heterocycles. [8-11]. Herein, we report the sodium sulfide-promoted reaction of 2-aminobenzamide and benzyl alcohols with elemental sulfur: A novel approach with 2-aryl-quinazolin-4(*3H*).

2. Content

2.1. Experiments

2.1.1. Chemicals

All reagents and solvents were of analytical grade purchased from commercial suppliers and used directly without further purification. Flash column chromatography was performed using silica gel (Kieselgel 60, 230-400 mesh, Merck) and thin-layer chromatography (TLC) was performed using a precoated silica gel 60 F254 (0.25 mm, Merck). Reactions were monitored by TLC (detection with UV light).

2.1.2. Instrumentation

The ^{1}H NMR (600 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6 on Bruker AV-600 spectrometer with TMS as an internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution ESI mass spectra were obtained on a SCIEX X500R QTOF high-resolution mass spectrometer.

2.1.3. The general process for the synthesis of 2-aryl-quinazolin-4(*3H*)-one derivatives (3) from 2-aminobenzamide (1) and benzyl alcohol (2)

A mixture of 2-aminobenzamide **1** (1 mmol), sulfur (1.5 mmol), benzyl alcohols (**2**) (1.2 mmol), $Na_2S.5H_2O$ (1.2 mmol), and DMSO (0.5 mL) was heated in a 7 mL glass test tube sealed with a rubber stopper under an argon atmosphere at 140 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel.

2-phenylquinazolin-4(3H)-one (**3a**) [12]: Purification of the crude mixture by column chromatography on silica gel (*n*-hexane:acetone = 97:4) obtains **3a** compound as a white solid (Yield: 86%). ^{1}H NMR (DMSO, 600 MHz): δ (ppm) 12.56 (s, 1H); 8.20 (d, J = 6.6 Hz, 2H); 8.18 (d, J = 7.8 Hz, 1H) 7.85 (t, J = 8.4 Hz, 1H); 7.76 (d, J = 7.8 Hz, 1H); 7.64 - 7.51 (m, 4H).

2-(p-tolyl)quinazolin-4(3H)-one (**3b**) [13]: Purification of the crude mixture by column chromatography on silica gel (*n*-hexane:acetone = 97:4) obtains **3b** compound as a white solid (Yield: 65%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 11.36 (s, 1H); 8.25 (dd, J = 7.9; 1.5 Hz; 1H); 8.07 (d, J = 8.3 Hz; 2H); 7.78 - 7.68 (m, 2H); 7.42 (ddd, J = 8.1; 6.8; 1.4 Hz; 1H); 7.30 (d, J = 7.9 Hz; 2H), 2.39 (s, 3H).

2-(4-methoxyphenyl)quinazolin-4(3H)-one (**3c**) [14]: Purification of the crude mixture by column chromatography on silica gel (*n*-hexane:acetone = 97:5) obtains **3c** compound as a white solid (Yield; 31%). ^{1}H NMR (DMSO, 600 MHz): δ (ppm) 12.38 (s, 1H); 8.18 (d, J = 8.4 Hz; 2H); 8.13 (d, J = 7.8 Hz; 1H); 7.81 (t, J = 8.4 Hz, 1H); 7.70 (d, J = 7.8 Hz; 1H); 7.48 (t, J = 7.2 Hz; 1H); 7.08 (d, J = 8.4 Hz; 2H); 3.84 (s, 3H).

2-(4-(tert-butyl)phenyl)quinazolin-4(3H)-one (**3d**) [14]: Purification of the crude mixture by column chromatography on silica gel (*n*-hexane:acetone = 97:5) obtains **3d** compound as a white solid (Yield: 28%). ^{1}H NMR (DMSO, 600 MHz): δ (ppm) 12.47 (s, 1H); 8.20 - 8.11 (m, 3H); 7.83 (ddd, J = 8.5; 7.0; 1.6 Hz, 1H); 7.73 (d, J = 8.2 Hz; 1H); 7.57 (d, J = 8.5 Hz; 2H); 7.51 (ddd, J = 8.1; 7.1; 1.2 Hz, 1H); 1.33 (s, 9H).

2-(4-chlorophenyl)quinazolin-4(3H)-one (**3e**) [14]: Purification of the crude mixture by column chromatography on silica gel (*n*-hexane:acetone = 97: 5) obtains **3e** compound as a white solid (Yield: 23%). ^{1}H NMR (DMSO, 600 MHz): δ (ppm) 12.60 (s, 1H); 8.21 (d, J = 8.7 Hz; 2H); 8.16 (d, J = 8.0 Hz, 1H); 7.88 - 7.82 (m, 1H); 7.75 (d, J = 8.1 Hz, 1H); 7.63 (d, J = 8.6 Hz, 2H); 7.54 (t, J = 7.5 Hz, 1H).

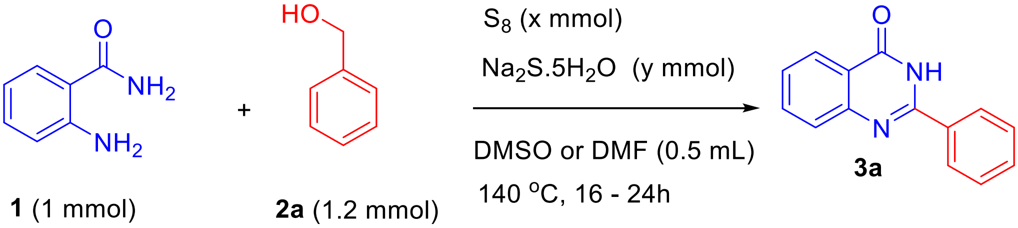
2.2. Results and discussion

We began our efforts by examining the condensation reaction of 2-aminobenzamide (**1**) with benzyl alcohol (**2a**) in the presence of elemental sulfur as a catalyst (Table 1). Firstly, without sodium sulfide, the heat of a mixture of **1** and **2a** with sulfur (1 equiv.) in DMSO at 140 °C resulted in the formation of **3a** with a low yield (16%) (Entry 1). Sodium sulfide was previously [15] identified as an excellent sulfur activator in DMSO, we observed the promotion of the reaction with a small amount of $Na_2S.5H_2O$ (0.4 equiv., entry 3). When the amount of sodium sulfide was increased to 1.0 equivalent (Entry 3), the reaction yield increased significantly (75% yield). The reaction yield did not change with decreasing reaction time (16 h, entry 4).

Replacing DMSO with DMF significantly reduces the reaction yield, which demonstrates the co-oxidative role of DMSO in the reaction with sulfur [16, 17]. The reaction yield increased slightly when increasing the amount of $Na_2S.5H_2O$ to 1.2 equiv. (77%, entry 6). However, when continuing to increase the amount of $Na_2S.5H_2O$, the reaction yield decreased (Entry 7, 8).

Although DMSO was thought to act as a co-oxidant, a reaction with low sulfur (Entry 9) results in lower yields. The reaction worked well with a slight excess of sulfur (Entry 10). Finally, excess sulfur leads to a decrease in the reaction yield (2.0 equiv., entry 11).

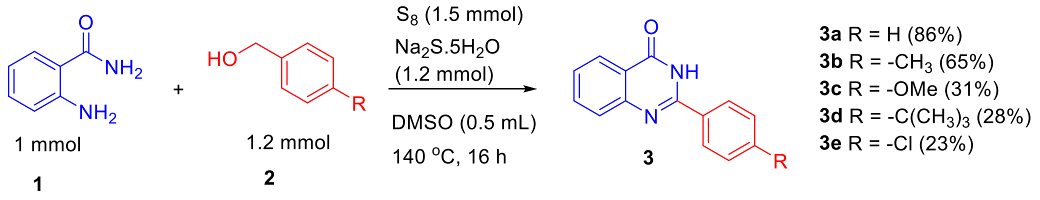
Table 1. Optimization of the Reaction Conditions



Entry[a]	x	y	DMSO or DMF	Time (h)	Yield (%)[b]
1	1.0	0	DMSO	24	16
2	1.0	0.4	DMSO	24	41
3	1.0	1.0	DMSO	24	75
4	1.0	1.0	DMSO	16	74
5	1.0	1.0	DMF	16	29
6	1.0	1.2	DMSO	16	77
7	1.0	1.4	DMSO	16	51
8	1.0	1.6	DMSO	16	52
9	0.5	1.2	DMSO	16	39
10	**1.5**	**1.2**	**DMSO**	**16**	**86**
11	2.0	1.2	DMSO	16	54

*[a] Reaction conditions: 2-aminobenzamide **(1)** (1 mmol, 136 mg), benzyl alcohol **(2a)** (1.2 mmol, 129 mg), S_8 (x mmol, 32 mg/mmol), $Na_2S.5H_2O$ (y mmol), DMSO or DMF (0.5 mL), 140 °C, 16 - 24 h. [b] Isolation yield.*

Under the optimized reaction conditions. We have synthesized five 2-aryl-4(3*H*)-quinazolinone derivatives with yields from 23% to 86% (Scheme 2). In general, condensation of the substituted benzyl alcohols (**3b-e**) gives lower yields than the unsubstituted benzyl alcohol (**3a**). Only the reaction of 4-methylbenzyl alcohol with the $-CH_3$ electron donating group on the aromatic ring proceeded smoothly to give the desired products in good yields (65%, **3b**). The benzyl alcohols containing the bulky substituent (**3d**) and the chloro group (**3e**) do not appear to be well tolerated for this condition. Research on optimizing reaction conditions to extend the scope of synthesis with benzyl alcohols bearing different substituents is continuing in our laboratory.



Scheme 2. Synthesis of 2-aryl-4(3H)-quinazolinone derivatives

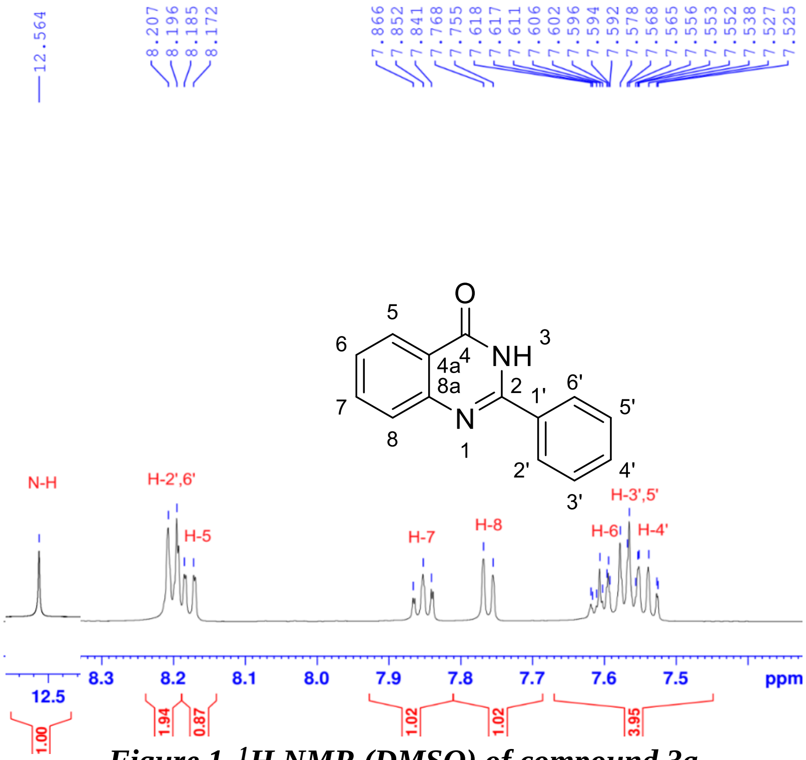


Figure 1. ^{1}H NMR (DMSO) of compound 3a

The structures of the synthesized compounds were determined based on ^{1}H NMR spectra by comparison with literature data. The assignment of clear NMR spectra of 2-phenylquinazolin-4(*3H*)-one (**3a**) has been published in the literature (Table 2) [18]. As shown in Figure 1, we compared and attributed the spectrum of compound (**3a**) as follows: singlet signal at 12.56 ppm is characteristic of N-H proton, doublet signal at 8.20 ppm with coupling constant J = 6.6 Hz with 2H is characteristic of phenyl proton at *ortho* position H-2', H-6', doublet signal at 8.18 ppm (J = 7.8 Hz; 1H) is assigned to proton H-5, a triplet resonance signal at 7.85 ppm (J = 8.4 Hz, 1H) is assigned to proton H-7, resonance signal at 7.76 ppm (J = 7.8 Hz, 1H) is assigned to the proton H-8. The multiplet signal in the range of 7.64 - 7.51 ppm consists of four protons H-6, H-3', H-5', and H-4'. Similarly, the structures of the **3b-e** derivatives were also determined by comparing the ^{1}H NMR spectra with the reference data.

Table 2. NMR spectrometric data of compounds 3a and 2-phenylquinazolin-4(3H)-one in DMSO-d_6

Position	**Compound 3a (DMSO-d_6, 600 MHz)**	**2-phenylquinazolin-4*(3H)*-one[18] (DMSO-d_6, 400 MHz)**
	δ_H, J (Hz)	δ_H
5	8.18 (d, J = 7.8 Hz, 1H)	8.19
6	7.64 - 7.51 (m, 1H)	7.54
7	7.85 (t, J = 8.4 Hz, 1H)	7.84
8	7.76 (d, J = 7.8 Hz, 1H)	7.76
2’, 6’	8.20 (d, J = 6.6 Hz, 2H)	8.22
3’, 5’	7.64 - 7.51 (m, 2H)	7.57
4’	7.64 - 7.51 (m, 1H)	7.60
N-H	12.56 (s, 1H)	12.47

3. Conclusions

In summary, we have discovered a novel, simple, metal- and solvent-free approach to synthesize 2-aryl-4(*3H*)-quinazolinone derivatives from 2-aminobenzamide and benzyl alcohol with modest to fairly good yields (23 - 86%). Readily accessible starting materials were applied as substrate in the presence of inexpensive elemental sulfur as an oxidizing agent and $Na_2S.5H_2O$ as a sulfur activator, and DMSO acting as a co-oxidant. The scope of this reaction is being carried out in our laboratory.

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