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Authors: Thanh Binh Nguyen, Jing-ya Hou, and pascal retailleau

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Sulfur-Promoted Synthesis of 2-Aroylquinazolin-4(3*H*)-ones by Oxidative Condensation of Anthranilamide and Acetophenones

Thanh Binh Nguyen,* Hou Jing-ya, and Pascal Retailleau

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette, France
Email: thanh-binh.nguyen@cnrs.fr

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Abstract. A sulfur-promoted three-component reaction of isatoic anhydride, primary aliphatic or aromatic amines, and acetophenones leading to densely substituted 3-substituted 2-aroylquinazolin-4(3*H*)-ones is reported. The key step involves a cascade reaction of selective oxidation of the methyl group of the acetophenones, followed by a condensation with anthranilamides. The scope of the reaction is applicable to the synthesis of tryptanthrin and various 3-unsubstituted 2-aroylquinazolin-4(3*H*)-ones.

Keywords: sulfur; anthranilamide; acetophenone, DMSO; oxidative condensation

Aza heterocycles constitute core structural components in a variety of natural products and biologically active compounds. Quinazolin-4(3*H*)-one scaffold in particular are not only ubiquitous in biologically active molecules[1] but also present in a diverse set of natural products (Figure 1).[2] Consequently, an increasing number of new methodologies have been developed to enhance the occurrence of the quinazolin-4(3*H*)-one scaffold in corporate compound collections for biological evaluations.[3] In order to increase the lipophilicity as well as the activity of quinazolin-4(3*H*)-ones, one of the simplest strategies is to incorporate an alkyl or aryl substituents to the N-3 position.[4]

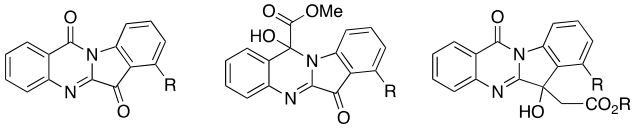
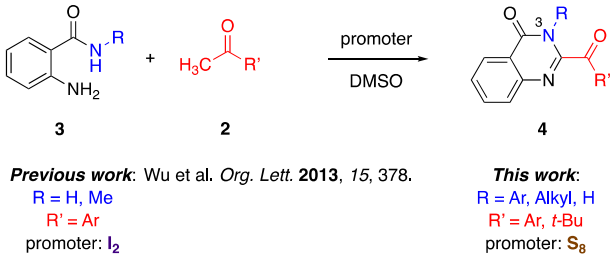


Figure 1. Selected 2-Aryl-3-Aroylquinazolin-4(3*H*)-ones

Herein, we describe a convenient access to 3-substituted 2-aroylquinazolin-4(3*H*)-ones **4** base on three component one-pot two-step reaction of isatoic anhydride, primary aliphatic or aromatic amines, and acetophenones **2** promoted by elemental sulfur. To the best of our knowledge, this is the first report of general sulfur-promoted oxidative coupling between weakly nucleophilic and sterically hindered *N*-substituted 2-aminobenzamides with acetophenones. More importantly, we expand this concept to *N*-unsubstituted 2-aminobenzamides.

In 2013, Wu et al. reported an I_2/DMSO promoted oxidative coupling reaction between 2-aminobenzamides with acetophenones to provide a range of 3-unsubstituted 2-benzoylquinazolin-4-ones (Scheme 1).[5] Because of a side reaction between molecular iodine with 2-aminobenzamides leading to their 5-iodinated derivatives, the iodination step of acetophenones should be performed prior to the addition 2-aminobenzamides. Moreover, it appears that this approach is working well when the amide function of 2-aminobenzamides is not substituted. Indeed, the yields of *N*-methyl amides derivatives were described to be generally lower than that of their NH_2 amide analogues and no other larger substituents were reported.



Scheme 1. 2-Aroylquinazolin-4(3*H*)-ones **4** from Anthranilamides **3** and Methyl Ketones **2**

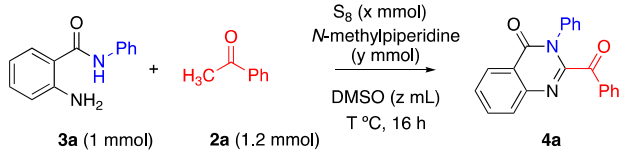
Here, we propose an alternative strategy based on the use of elemental sulfur[6] as an oxidant applicable to anthranilamides **3** bearing a wide range of alkyl and aryl substituent on the amide group.

For this purpose, we started the optimization studies based on the oxidative coupling reaction between 2-aminobenzanilide **3a** with acetophenone **2a** in the presence of elemental sulfur (twice the stoichiometric amount) as oxidant (Table 1). The

10.1002/adsc.201900371

reaction between the three components under neat condition (entry 1) or in a small amount of DMSO at 100 ºC did not lead to the expected product **4a**. Gratifyingly, in the presence of *N*-methylpiperidine, which was previously identified as an excellent sulfur activator,[7] we observed the formation of quinazolinone **4a** (entry 3), especially in the presence of DMSO[4d] (entries 5-7). The reaction worked well with a slight excess of sulfur (entry 7). However, although DMSO was thought to act as co-oxidant, reaction with stoichiometric or sub-stoichiometric amount of sulfur (entries 8-9) resulted in lower yields. Finally, we found that the reaction is less efficient with lower *N*-methylpiperidine amount (entry 10) or at lower temperature (entry 11).

Table 1. Optimization of the Reaction Conditions



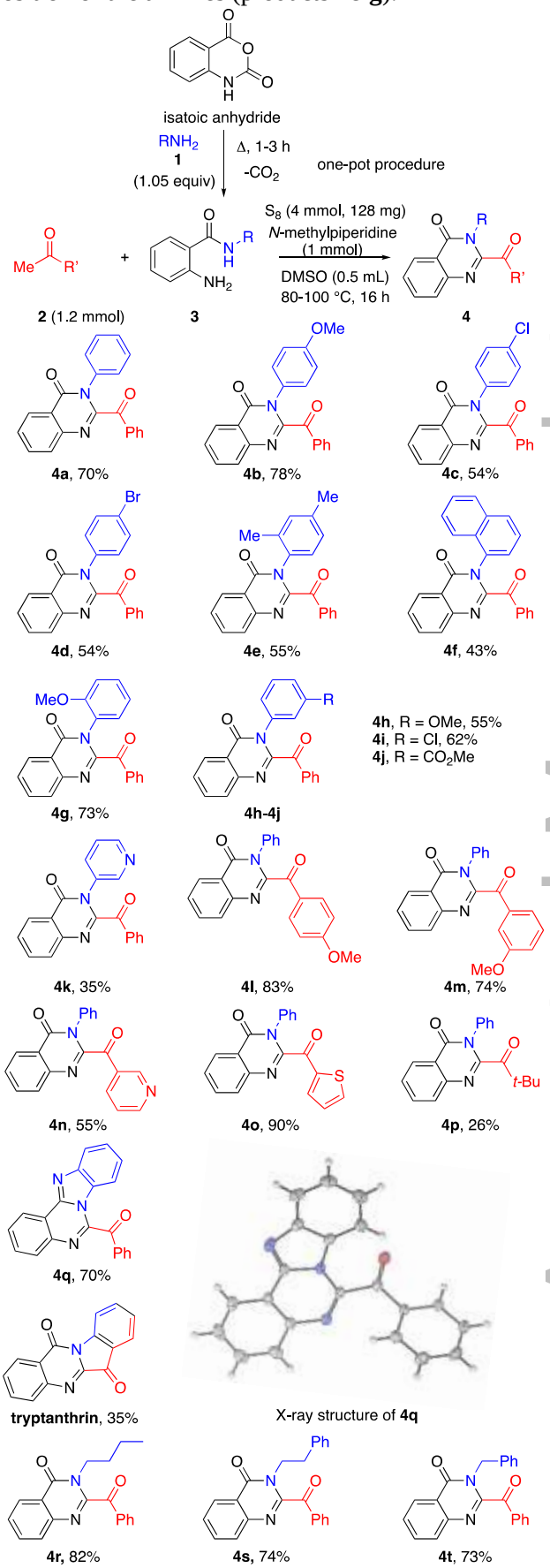
3a (1 mmol) **2a** (1.2 mmol) **4a**

Entry[a]	x	y	z	Temp (°C)	Yield (%)[b]
1	6	0	0	100	0[c]
2	6	0	0.1	100	0[c]
3	6	1	0	100	25
4	6	1	0.1	100	45
5	6	1	0.2	100	67
6	6	1	0.5	100	70
7	**4**	**1**	**0.5**	**100**	**75**
8	3	1	0.5	100	67
9	2	1	0.5	100	35
10	4	0.5	0.5	100	45
11	4	1	0.5	80	38

[a] Reaction conditions: 2-aminobenzanilide **3a** (1 mmol, 212 mg), acetophenone **2a** (1.2 mmol, 144 mg), sulfur (x mmol, 32 mg/mmol), *N*-methylpiperidine (y mmol), DMSO (z mL), 80-100 °C, 16 h. [b] Isolated yield. [c] Determined by ^{1}H NMR.

Next, the optimized conditions (entry 7) were adapted to the syntheses of other quinazolinones **4** (Scheme 2). Since most of *N*-substituted 2-aminobenzanilides were not commercially available, we developed a convenient access to such compounds based on thermal, uncatalyzed and solvent-free reaction between isatoic anhydride with stoichiometric amounts of amine.[8]

The decarboxylative coupling with aromatic amines **1** with isatoic anhydride under solvent free conditions was performed at 130-150 °C for 1-3 h. Gratifying, once the process was completed, the CO_2 evolution ceased. Acetophenone, sulfur, *N*-methylpiperidine and DMSO were subsequently added and the reaction mixtures were further heated at 100 °C for 16 h. One-pot reaction of unsubstituted aniline led to the expected product **4a** in slightly lower yield (75% vs 70%). Similarly, *p*-anisidine provided the desired product **4b** in excellent yield. Gratifyingly, the optimal conditions were compatible with halogeno groups (products **4c**, **4d** and **4i**) and with sterically hindered substituent at the *ortho* position of the anilines (products **4e-g**).



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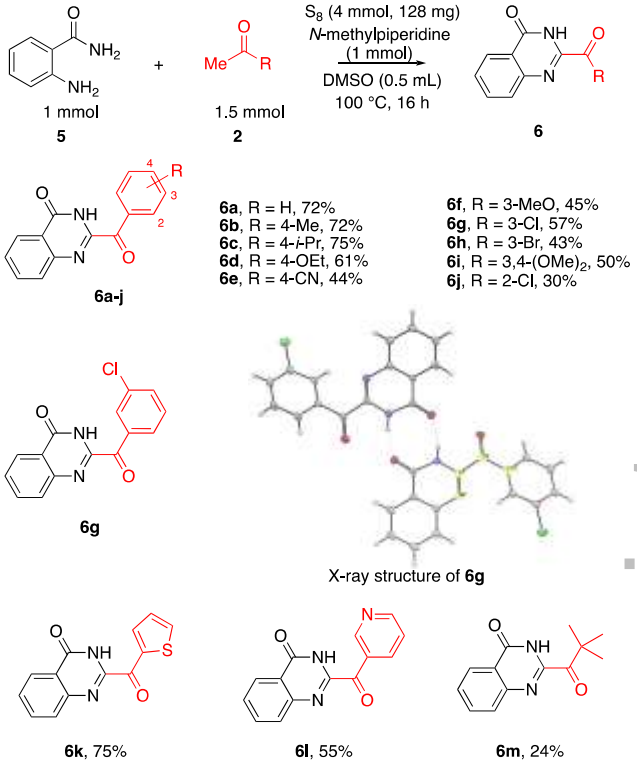
Scheme 2. One-pot Synthesis of Quinazolinones **4** from Isatoic Anhydride, Amines **1** and Methyl Ketones **2**

Importantly, heteroaromatic amine such as 3-aminopyridine could successfully be incorporated into the quinazolinone **4i**, albeit with a diminished yield. Subsequently, the one-pot protocol was applicable to substituted acetophenones and their heteroaromatic analogues 3-pyridyl and 2-thienyl to provide products **4l**-**4o** in reasonable yields. Although the reaction of alkyl methyl ketones (2-pentanone or 2-heptanone) seems to be complicated (results not shown), we were able to obtain the product **4p** from pinacolone. In this case, despite the low yield, the reaction mixture remained clean, suggesting undoubtedly that the *t*-butyl group slowed the conversion process.[9] When *o*-phenylenediamine was used as starting amine, fused tetracyclic compound **4q** was formed in good yield. Its structure was confirmed via X-ray crystallography.

Interestingly, our strategy could be applied to the synthesis of tryptanthrin. For this purpose, *o*-aminoacetophenone was used as the amine component. Due to unfavorable electron withdrawing effect of the acetyl group as well as its steric hindrance, the decarboxylative coupling step should be performed at 160 ºC to ensure significant CO_2 evolution. Subsequent intramolecular oxidative condensation providing tryptanthrin could be achieved under the standard conditions. Despite low global yield in which the first step of formation of the corresponding anthranilamide could be improved, this result showed that the reaction could be realized in an intramolecular version.

When primary aliphatic amines were used as the amine components, the formation of the corresponding substituted anthranilamides could be performed at significantly lower temperatures (rt-60 ºC). Subsequent oxidative condensation with acetophenone led to the final products **4r**-**4t** in high yields.



Scheme 3. Synthesis of NH Quinazolinones **6**

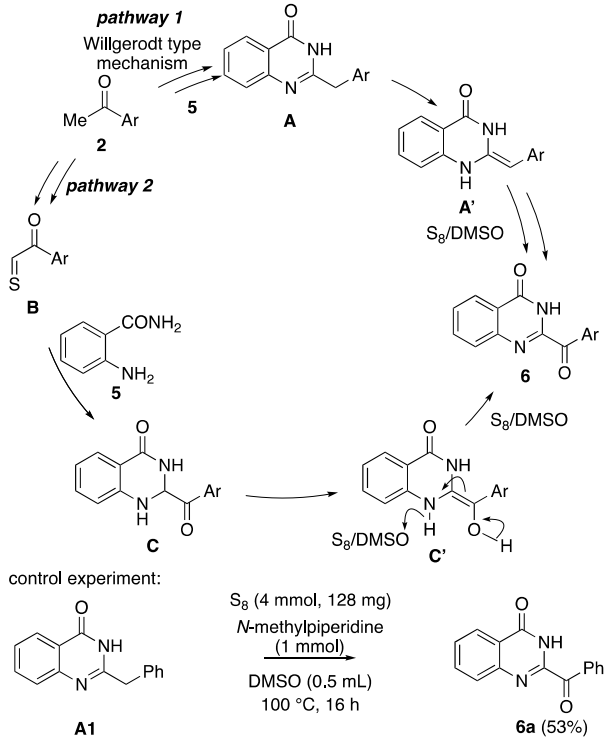
At this stage, with highly general and simple conditions in place, we focused our attention on the reaction of *N*-unsubstituted anthranilamides **6** (Scheme 3). Thus, we employed this substrate in the reaction with a range of acetophenones.

This approach led to the synthesis of 3-NH-quinazolin-4-ones **6a**-**6i** in moderate to good yields (43–75%). In general, acetophenone itself as well as its analogues *p*-substituted by an electron donating group gave better yields (**6a**-**6d**). On the other hand, *p*-cyanoacetophenone displayed lower reactivity (product **6e**). Although the byproduct of the reaction, i.e. hydrogen sulfide, is known to add to the nitrile group to yield thioamide, such a reaction did not happen under the present conditions. Other *m*-substituted acetophenones afforded the expected quinazolin-4-ones **6f**-**6i** in moderate yields. The structure of quinazolinone **6g** derived from *m*-chloroacetophenone was confirmed unambiguously by X-ray crystallography. Interestingly, the reaction proceeded in similar fashion with other heteroaromatic methyl ketones.

Introducing an *o*-chloro group on the aromatic ring of the acetophenone moiety afforded the products in lower yield (**6j**). This observation suggested that the efficiency of the oxidative coupling process depends also on the steric hindrance of the methyl ketone moiety.[10] Additionally, heteroaryl methyl ketones such as 2-acetylthiophene and 3-acetylpyridine afforded the corresponding products **6k**-**6l** in reasonable yields. Once again, pinacolone exhibited a lower reactivity. It should be however noted that such

10.1002/adsc.201900371

an example was not reported with molecular iodine-promoted method.[6]



Scheme 4. Proposed Mechanism

Based on the results previously reported by our group,[7] we proposed a plausible mechanism depicted in Scheme 4. The formation of quinazolinone **6** could proceed via two possible pathways. In the first pathway,[7c] methyl ketone **2** would react with sulfur activated by *N*-methylpiperidine according to Willgerodt type mechanism. While its methyl group is oxidized and trapped with anthranilamide **5** to form an amidine moiety, its ketone group is reduced into a methylene group to yield quinazolinone **A**.[11] Oxidation of the benzylic by S/DMSO would lead to the final product **6**. Alternatively, the methyl group of ketone **2** could be directly oxidized by sulfur to aldehyde **B**, which could subsequently condense with **5** to provide aminal **C** and then quinazolinone **6**. In both pathways, the oxidation of **A** and **C** to **6** could be favored by the formation of the tautomers **A'** from **A** and **C'** from **C**.

To confirm the oxidation step of **A** to **6**, **A1** (Ar = Ph) was synthesized independently[12] and allowed to react under the same conditions. The formation of **6a** in moderate yield in the presence of both sulfur and DMSO as oxidants suggested the feasibility of this pathway.

In summary, we have developed a one-pot two-step three-component reaction of isatoic anhydride, primary aliphatic or aromatic amines **1**, and methyl ketones **2** (acetophenones or pinacolone) promoted by elemental sulfur to provide a range of 3-substituted 2-aroylquinazolin-4(3*H*)-ones **4**. The use of *o*-aminoacetophenone as both amine and methyl ketone component has provided a proof-of-concept of our strategy in the one-pot synthesis of natural quinazolinone tryptanthrin. This new procedure of sulfur-promoted oxidative coupling of anthranilamide **5** with methyl ketones **2** was also successfully utilized to prepare NH 2-aroylquinazolin-4-ones **6**. Further exploration of new reactivities of elemental sulfur in organic chemistry and applications are currently in progress in our laboratory.

Experimental Section

One-pot procedure for the synthesis of quinazolinones 4 from isatoic anhydride, amines 1 and methyl ketones 2

From aromatic amines: A mixture of isatoic anhydride **1** (1 mmol), and aromatic amine (1.05 mmol) was heated with magnetic stirring at 130-150 °C for 1-3 h in a 7-mL glass test tube closed with a rubber septum under an argon atmosphere. The CO_2 gas formed during the course of the reaction was evacuated by mean of a rubber argon balloon. When the evolution of CO_2 ceased, sulfur (4 mmol, 128 mg), methyl ketone (1.2 mmol), *N*-methylpiperidine (1 mmol, 99 mg), and DMSO (0.5 mL) were added and the reaction tube was closed again, flushed with argon and heated at 100 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel.

From aliphatic amines: Aliphatic amine (1.05 mmol) was added to a mixture of isatoic anhydride 1 (1 mmol) in DMSO in a 7-mL glass test tube. The resulting mixture was stirred at rt for 5-10 min, the tube was next closed with a rubber septum under an argon atmosphere. The CO_2 gas formed during the course of the reaction was evacuated by mean of a rubber argon balloon. The tube was heat at 60 °C. When the evolution of CO_2 ceased, sulfur (4 mmol, 128 mg), methyl ketone (1.2 mmol), and *N*-methylpiperidine (1 mmol, 99 mg) were added and the reaction tube was closed again, flushed with argon and heated at 100 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel.

Procedure for the synthesis of quinazolinones 6 from anthraniliamide 5 and methyl ketones 2

A mixture of anthranilamide **5** (1 mmol 136 mg), sulfur (4 mmol, 128 mg), methyl ketone **2** (1.2 mmol), *N*-methylpiperidine (1 mmol, 99 mg) and DMSO (0.5 mL) was heated in a 7-mL glass test tube under an argon atmosphere at 100 °C for 16 h. The reaction mixture was purified by column chromatography on silica gel.

CCDC-1881910 and CCDC-1881911 (compounds **6g** and **4p** respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] The reaction of cyclohexyl methyl ketone resulted only in a trace amount of the expected product, possibly due to the reaction on the enone form on its cyclohexyl moiety.

[10] A similar reaction with *o*-methoxyacetophenone instead of *o*-methoxyacetophenone resulted only in a trace amount of the expected product and confirmed this hypothesis. No effort has been made to isolate the product in this case.

[11] We observed frequently the formation of products **A** in the reaction mixtures by their characteristic 1H NMR signals of the methylene groups (singlet at about 3.7-4.0 ppm). We were however unable to isolate such products.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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