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Base-Catalyzed Multicomponent Access to Quinoxalin-2-thiones from *o*-Phenylenediamines, Aryl Ketones and Sulfur

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3-Arylquinoxaline-2-thiones were conveniently synthesized via three-component oxidative condensation of acetophenones with *o*-phenylenediamines and sulfur in DMSO in the presence of piperidine as a catalyst. The products could be readily isolated from the reaction mixture by simple precipitation and washing with methanol. This set of reaction conditions applied to higher homologs of acetophenones as well as benzyl phenyl ketones led to 2,3-di-*C*-substituted quinoxalines. Further functionalization of 3-phenylquinoxaline-2-thione via reaction on the thione group could be readily performed to provide quinoxaline derivatives in good yields.

Quinoxalines are important heterocyclic building-blocks found in useful molecules ranging from biologically and pharmaceutically important compounds to materials. Consequently, significant efforts aiming at developing more efficient synthesis of quinoxalines and their derivatives have been made. Among the various quinoxalines, 3-arylquinoxaline-2-thione **3** and 2,3-di-*C*-substituted quinoxalines **5** have been considered as the most important examples, presumably due to their use as versatile synthetic intermediates, their unique biological activities¹ (**Q1-Q3**) as well as physical properties suitable for solar cell polymer development **Q4**,² fluorescent sensor **Q5**,³ optoelectronic devices **Q6**,⁴ and electrochromic materials **Q7**.⁵ Moreover, due to the rich reactivity of the thione group, especially when acting as a leaving group or nucleophilic center for further functionalization, quinoxaline-2-thione **3** could serve as versatile intermediates for quinoxaline derivatization, particularly 2-aminoquinoxalines (**Q8**)⁶ and quinoxalin-2-yl thioethers (**Q1** and **Q2**).⁷

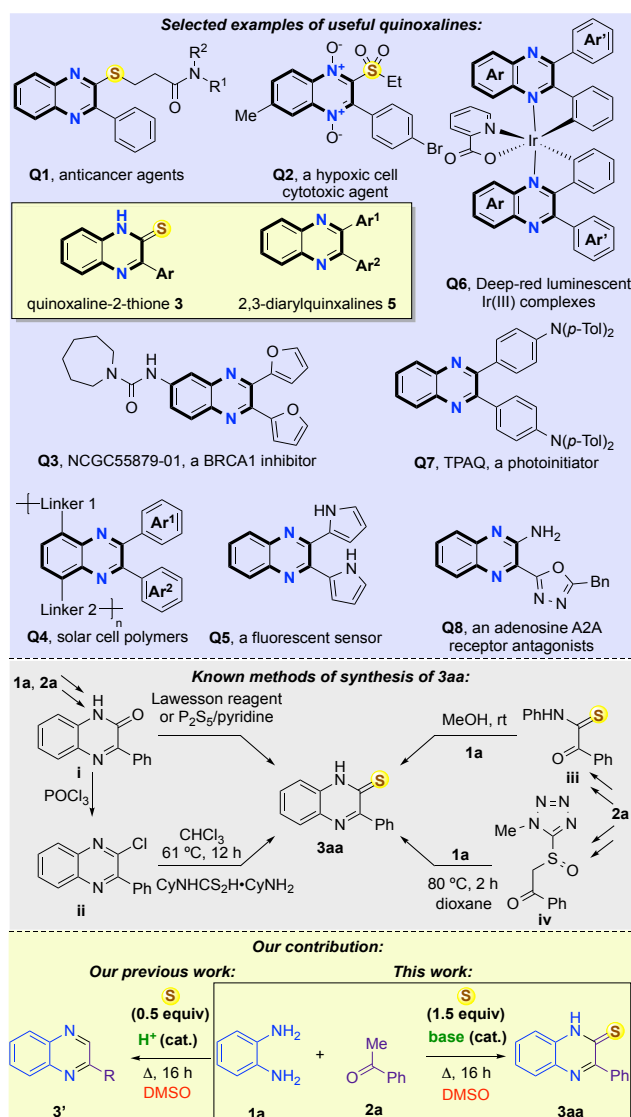


Figure 1. Background and Retrosynthetic Disconnection Design of Syntheses of Quinoxaline of Types **3** and **5**

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^c Le Quy Don Technical University, 236 Hoang Quoc Viet, Ha Noi, Vietnam Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

However, the existing methods often suffer from at least one of the following limitations, such as requirement of highly functionalized substrates,⁷ multi-step synthetic sequences,⁸ lack of structural diversity of target products as well as harsh/complex reaction conditions with low atom-/step-efficiency.⁹ For example, **3aa** could be synthesized from the corresponding lactam **i** using Berzelius reagent (P₂S₅)^{12b} or from chloride **ii**,^{1c} which was obtained from **ii** using POCl₃. It should be noted that both of these phosphorus reagents were highly reactive, moisture sensitive and low functional group tolerant. Alternatively, condensation of *o*-phenylenediamine **1a** with densely functionalized benzoyl derivatives **iii**^{12a,c} and **iv**⁸ were reported. In four cases, all the starting materials **i-iv** could be synthesized from acetophenones **2a** via multi-step sequences.

Generally, the synthesis of quinoxalines involves a non-redox condensation of *o*-phenylenediamines and 1,2-dicarbonyl moieties or synthetic equivalents.¹⁰ As is well known, using enolizable ketones, especially acetophenones, which are both inexpensive and structurally more available, in place 1,2-dicarbonyl moieties could circumvent all these drawbacks provided that mild oxidizing conditions is employed.

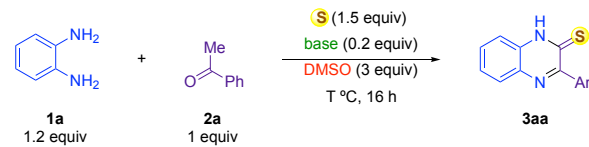
In view of the high specificity and selectivity of sulfur S₈ as an oxidant as well as its low cost, user-friendliness and synthetic versatility,¹¹ this substance could be an excellent candidate for the development of such desired conditions, especially for the synthesis of sulfur-containing derivatives while avoiding toxic, smelly and highly reactive sulfur reagents/precursors.¹²

Based on these considerations, we focus our attention on a three-component reaction of *o*-phenylenediamine **1a**, acetophenone **2a** and elemental sulfur to form 3-phenylquinoxaline-2-thione **3aa** (Table 1). Recently, we have reported on the catalytic activity of elemental sulfur in acidic medium of DMSO to trigger the oxidative condensation of *o*-phenylenediamines **1** with acetophenones **2** (R = Ar) leading to 2-arylquinoxalines **3'** (Figure 1).¹³ Interestingly, we found also that when a base was used as a catalyst instead of an acid, the formation of quinoxalines **3'** was significantly inhibited and sulfured quinoxalines **3aa** was obtained as the major product. Our first attempt performed under catalyst-free conditions using DMSO as an oxidant at 80 °C led to quinoxaline **3aa** as a yellow solid. Being sparingly soluble in methanol, **3aa** could be readily isolated from the reaction mixture by trituration/filtration with MeOH in 25% (entry 1).

Further screening of other organic nitrogen bases which were previously used to activate elemental sulfur^{Error! Bookmark not defined.} (*N*-methylpiperidine, triethylamine, DIPEA, *N*-methylmorpholine, pyridine, 3-picoline) (entries 3-8) showed that while weak bases were catalytically inefficient (entries 6-8), stronger bases could deliver **3aa** in reasonable yields (entries 3-5). Interestingly, piperidine was shown also to remarkably improve the reactivity (entry 9). This result was surprisingly interesting because in principle, the formation of **3aa** could be interfered by Willgerodt reaction of acetophenone and sulfur with piperidine to yield *N*-thiophenylacetyl piperidine while consuming amine catalyst. Similarly, other secondary amines such as pyrrolidine, 2,2,6,6-tetramethylpiperidine, dibutylamine (entries 10-12) as well as primary amines such as

octylamine and cyclohexylamine (entries 13-14) were also capable of catalyzing the transformation to **3aa** (entry 10-11). Additional screening confirmed the optimal temperature for the present reaction was 80 °C. Finally, we found that when the reaction was performed with only 1 equiv of sulfur, the isolated yield dropped significantly (entry 17).

Table 1. Screening of the Reaction Conditions

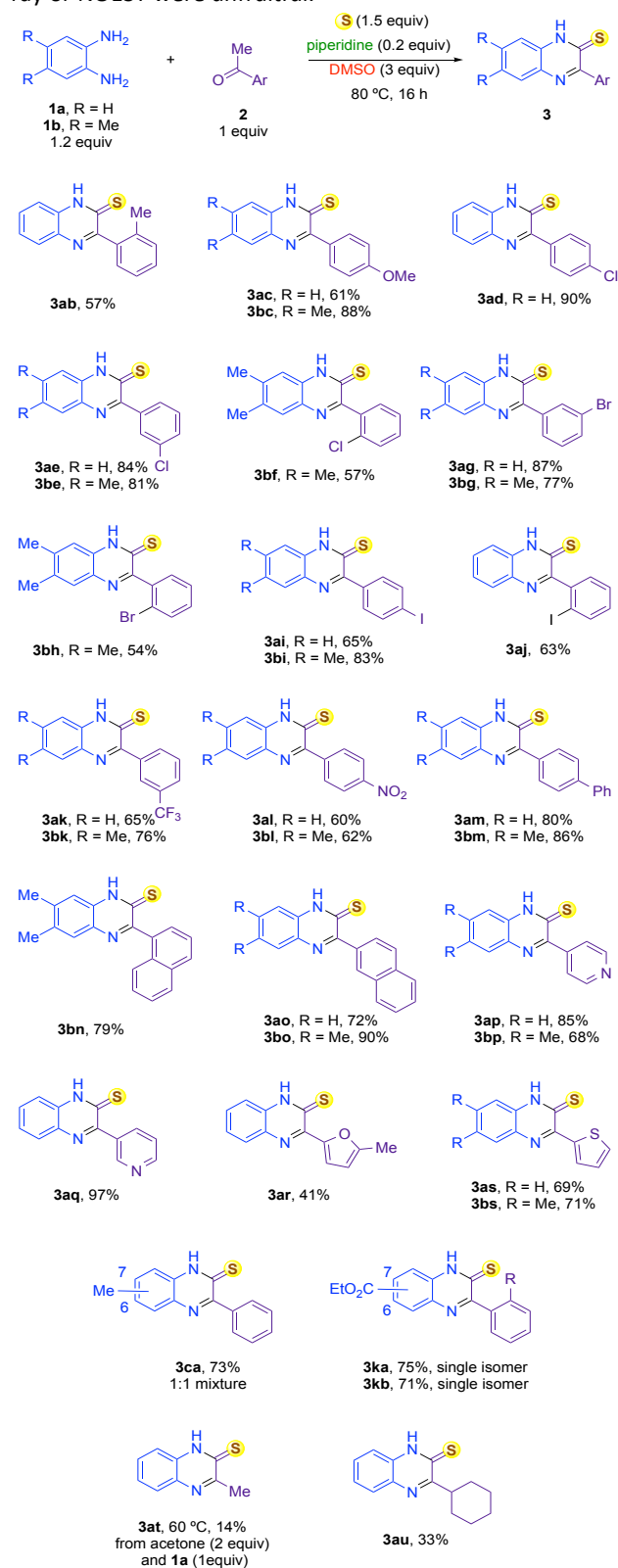


Entry ^a	Base catalyst	T (°C)	yield (%) ^b
1	-	80	25
2	DABCO	80	68
3	<i>N</i> -methylpiperidine	80	60
4	triethylamine	80	76
5	DIPEA	80	55
6	<i>N</i> -methylmorpholine	80	44
7	pyridine	80	40
8	3-picoline	80	42
9	piperidine	80	77
10	pyrrolidine	80	60
11	2,2,6,6-tetramethylpiperidine	80	65
12	dibutylamine	80	62
13	octylamine	80	67
14	cyclohexylamine	80	69
15	piperidine	60	32
16	piperidine	100	65
17 ^c	piperidine	80	42

^a Reaction conditions: *o*-phenylenediamine **1a** (1.0 mmol, 108 mg, 1.2 equiv), acetophenone **2a** (1.2 mmol, 144 mg), sulfur (1.5 equiv, 1.5 mmol, 48 mg), base (0.2 mmol, 0.2 equiv) in DMSO (0.2 mL), T °C, 16 h. ^b Isolated yield unless otherwise noted. ^c Determined by ¹H NMR of the crude mixture. ^c Reaction performed with 1 equiv of sulfur.

The scope of the aryl ketones was next examined using the optimized conditions described in Table 1, entry 9. As depicted in Scheme 1, the reaction conditions were suitable for the synthesis of 2-arylquinoxalines **3** bearing functional groups. *o*-Methyl and electron donating group such as methoxy (**3ac**, **3bc**) showed good reactivity. Various halogenated derivatives (Cl, Br, I, **3ad**, **3ae**, **3be**, **3bf**, **3ag**, **3bg**, **3bh**, **3ai**, **3bi** and **3aj**), especially those with *o*-halo substituents could be obtained in reasonable yield. These halogens are particularly useful for further functionalization. Acetophenones bearing electron withdrawing groups (CF₃, NO₂) reacted also in the same manner, leading to quinoxalines **3ak**, **3bk** and **3al**, **3bl**. Quinoxaline substituted by a biphenyl (**3am**, **3bm**), naphthyl (**3bn**, **3ao**, **3bo**) or hetaryl moiety (pyridyls **3ap**, **3bp**, **3aq**), furan (**3ar**) and 2-thienyl (**3ao-3bo**) could be also easily obtained using this set of conditions. When 4-methyl-*o*-phenylene **1c** was allowed to react with acetophenone **2a**, the expected product **3ca** was formed as a nearly equivalent mixture of both possible regioisomers. On the other hand, when *o*-phenylenediamine bearing an electron

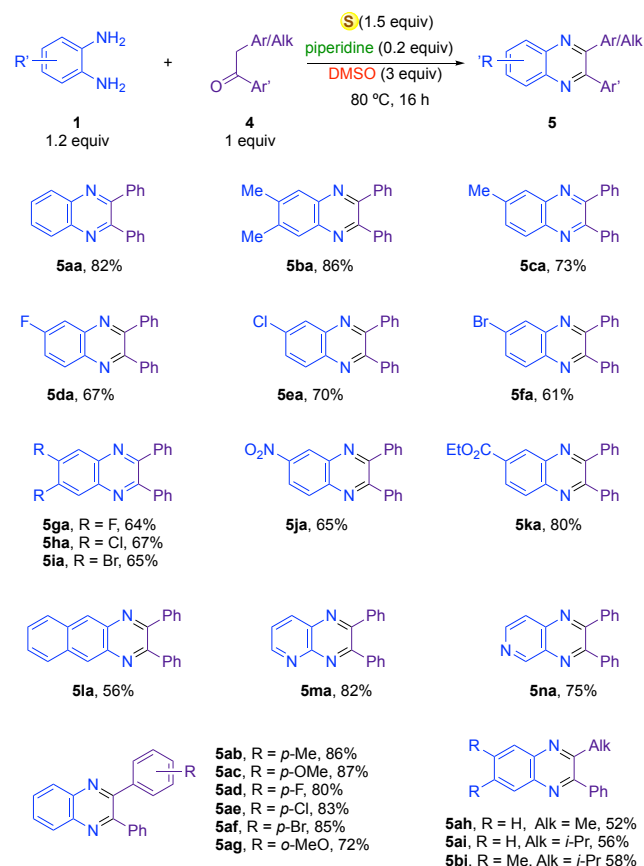
withdrawing group such as 4-ester derivative **1k** was used with acetophenones **2a** and **2b**, the desired products **3ka** and **3kb** were obtained as a single regioisomer in both case. Unfortunately, our effort in determining regiochemistry by X-ray or NOESY were unfruitful.

Scheme 1. Scope of the Reactions between **1** and **2**

Finally, aliphatic methyl ketones exhibited lower reactivity, resulting in the expected products in lower yields. In case of acetone, the reaction was performed at lower temperature with excess acetone to compensate loss due to its high volatility. It should be emphasized that all the quinoxaline-2(1H)-thione **3** described here could be readily isolated by dilution of the reaction mixtures, followed by filtration and washing with methanol.

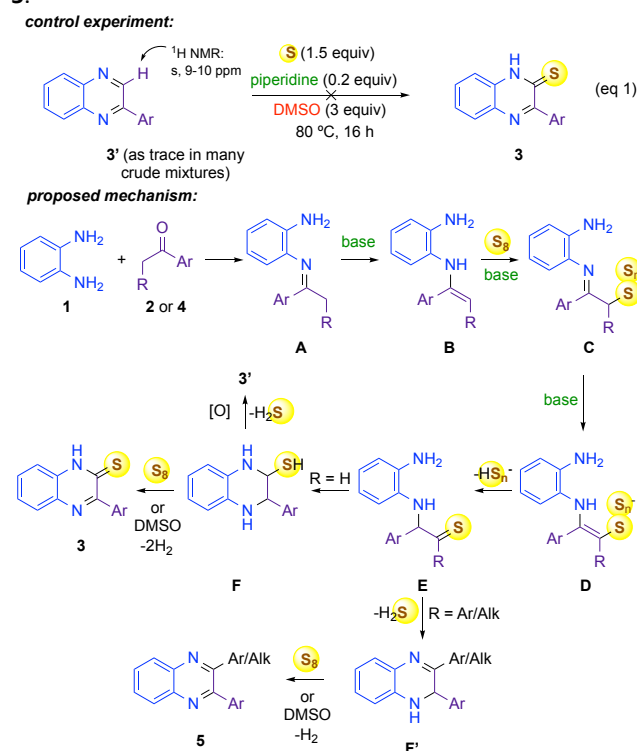
At this stage, we extended this set of optimized reaction conditions to acetophenone derivatives bearing an α -aryl or α -alkyl group **4**. Due to this substitution pattern, which is not intuitively suitable for the formation of quinoxaline structure, 2,3-di-C-substituted quinoxalines **5** were formed as summarized in Scheme 2. A wide range of *o*-phenylenediamines **1a-1n**, bearing alkyl, halogen, nitro, ester, benzo or pyridine groups exhibited excellent reactivity with deoxybenzoin **4a** to provide 2,3-diphenylquinoxaline derivatives **5aa-5ka** as well as the benzo **5la** and aza analogs **5ma-5na** in moderate to good yields. Similar results were also observed with deoxybenzoin **4b-4g** bearing two different aromatic rings with *o*-phenylenediamine **1a**, providing quinoxalines **5aa-5ag** in good yields.

We also examined the reactivity of aryl ketones **4h-4l** with longer alkyl chains. Propiophenone **4h** as well as its higher analog isovalerophenone **4i** reacted with *o*-phenylenediamine **1a,b** under the standard conditions to the expected 2-phenyl-3-alkylquinoxalines **5ah, 5ai** and **5bi** in moderate yields.

Scheme 2. Reactions of **1** with Aryl Ketones **4**

To give an insight into the reaction pathway, we envisioned many possibilities. A close investigation of many crude reaction mixtures by ^1H NMR spectra showed that 2-aryl-3-hydroquinoxalines **3'** were present as a minor component (thanks to their 3-H proton singlet signal between 9-10 ppm), suggesting that **3'** could be intermediate of the formation of **3** (Scheme 3). However, a control experiment performed by heating **3'** with elemental sulfur and piperidine in DMSO under the standard conditions (eq. 1) resulted did not lead to any change of **3'**, invalidating this hypothesis.

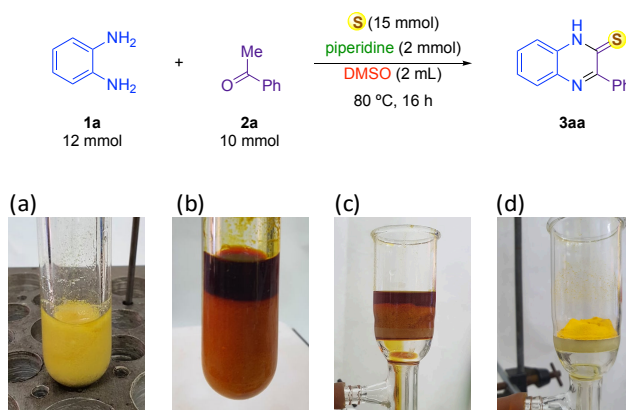
From this confirmation and on the basis of the previous results,¹⁴ a plausible mechanism is described. An initial condensation of amine **1** with ketone **2** or **4** would provide imine **A**, equilibrating with its enamine **B** via an amine-catalyzed process. The resulting enamine **B** could undergo sulfuration by sulfur to polysulfane **C**, which could tautomerize to enamine **D** and then thioaldehyde **E** after a desulfuration. Cyclization of **E** led to benzopiperazine **F** (R = H), readily dehydrogenated to **3** by either sulfur or DMSO. As a side product, quinoxaline **3'** would be formed if **F** underwent dehydrosulfuration before oxidation. It is clear that the presence of a base, which can deprotonate the mercapto function of **F**, could limit such a pathway. On the other hand, when acetophenone bearing an aryl or alkyl group on the alpha position was used, the cyclization step would proceed with elimination of H_2S to give **F'**, readily aromatized to **5**.



Scheme 3. Proposed Reaction Mechanism

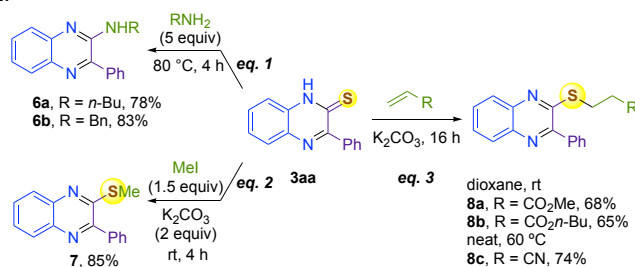
In order to demonstrate the robustness of our method, the three-component synthesis of quinoxaline-2-thione **3aa** starting from *o*-phenylenediamine **1a**, acetophenone **2a** and sulfur was performed on a gram scale (10 mmol). The reaction

under standard conditions afforded the desired products **3aa**, which was easily isolated by trituration/filtration with methanol in 76% (Scheme 4).



(a) reaction mixture before heating
(b) reaction mixture after heating and dilution with MeOH
(c) filtration and (d) dried product.
Scheme 4. Gram-scale Synthesis of **3aa**

From inexpensive and readily prepared in large scale quinoxaline-2-thione **3aa**, we explored new possibilities for rapid transformation to useful products with some encouraging initial results presented in Scheme 5. First, we found that the thione group could be readily displaced as **3aa** reacted readily with aliphatic primary amines such as butylamine, benzylamine under neat conditions upon heating at 80 °C without any added catalyst, leading to 2-amino derivatives **6a,b** (eq. 1). Second, the nucleophilicity of the thione group could be exploited by via nucleophilic substitution with iodomethane, providing methylthio ether **7** (eq. 2) or Michael addition with various acceptors such as acrylates esters and acrylonitrile, yielding adduct **8a-c**. These high yielding transformations under simple conditions are undoubtedly very practical and could be applied to the synthesis of **Q1**, **Q2** and **Q8** analogs presented in Scheme 1.

Scheme 5. Further Functionalization of **3aa**

Conclusions

In conclusion, we have developed a robust three-component reaction for the synthesis of 3-arylquinoxaline-2-thiones **3** via oxidative three-component condensation of acetophenones **2** with *o*-phenylenediamines **1** and elemental sulfur catalyzed by

piperidine with DMSO as an oxidant. In all cases tested, the products could be readily obtained by simple treatment with methanol and filtration. This set of reaction conditions was successfully applied to higher homologs of acetophenones as well as benzyl phenyl ketones **4** in place of acetophenones **2** to provide 2,3-di-*C*-substituted quinoxalines **5**. The key advantages of this strategy is the use of inexpensive substrates and reagents, with operationally simple and mild reaction conditions that are amenable to large-scale production. Further transformations of quinoxaline-3-one **3aa** into useful products **6-8** showcased the utility of our developed reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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