



HAL
open science

Sulfur-Catalyzed Oxidative Condensation of Aryl Alkyl Ketones with o-Phenylenediamines: Access to Quinoxalines

Anh Le, Thi Thu Tram Nguyen, Quoc Anh Ngo, Thanh Binh Nguyen

► **To cite this version:**

Anh Le, Thi Thu Tram Nguyen, Quoc Anh Ngo, Thanh Binh Nguyen. Sulfur-Catalyzed Oxidative Condensation of Aryl Alkyl Ketones with o-Phenylenediamines: Access to Quinoxalines. *Advanced Synthesis and Catalysis*, 2022, 364 (16), pp.2748-2752. 10.1002/adsc.202200527 . hal-03859331

HAL Id: hal-03859331

<https://hal.science/hal-03859331>

Submitted on 18 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Sulfur-Catalyzed Oxidative Condensation of Aryl Alkyl Ketones with *o*-Phenylenediamines: Access to Quinoxalines

Le Anh Nguyen,^{b,c} Thi Thu Tram Nguyen,^d Quoc Anh Ngo,^{*b,c} and Thanh Binh Nguyen^{*a}

^a 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

^b Institute of Chemistry, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam

^c Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam

^d Department of Chemistry, Faculty of Science, Can Tho University of Medicine and Pharmacy, Vietnam
E-mail: thanh-binh.nguyen@cnrs.fr; ngoqanh@ich.vast.vn

Received: (will be filled in by the editorial staff)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

Abstract. While elemental sulfur has been largely used as oxidant or sulfurating agent, its role as a catalyst has not been developed. We report here its catalytic activity in the oxidative condensation of *o*-phenylenediamines with acetophenones in DMSO to provide quinoxalines. The method was also extended to α -tetralones, propiophenones (R = Me) as well as higher homologues (R = Et, *n*-Pr) in place of acetophenones, leading to a wide range of naphthoquinoxalines and 3-substituted 2-arylquinoxalines.

Keywords: sulfur catalysis; quinoxaline; DMSO

Quinoxalines are important heterocyclic scaffolds that present widely in useful molecules such as natural products, bioactive compounds,^[1] crop protection products^[2] as well as advanced materials.^[3]

Some representative examples were presented in Figure 1. Riboflavin **Q1**, also known as vitamin B₂, possesses a ribose-derived quinoxaline core fused with a uracil. Baimantuoluamide B in the flower of *Datura metel* L., was found to be a potential CDK4 inhibitor **Q2**.^[4] Chloroquinoxaline sulfonamide **Q3** is active against murine and human solid tumors.^[5] Diverse 2-Aryl substituted quinoxaline derivatives were demonstrated to display bioactivities, ranging from hypoxia activated prodrug **Q4**,^[6] DNA intercalator **Q5**^[7] to enzyme inhibitors **Q6**,^[8] **Q7**^[9] and **Q8-Q9**.^[10] **Q10** was found to be a promising PET imaging agent.^[11]

Rapid access to the target compounds from starting materials that are readily available in both quantity and structural diversity will not only accelerate the lead identification and optimization but also lower the production cost once the molecules are

commercialized. Although there are many synthetic methods to construct 2-aryl-substituted quinoxalines,^[1] most of them based on specifically functionalized starting materials with limited availability, thus required addition steps of synthesis, thus lower the global atom- and step-efficiency.

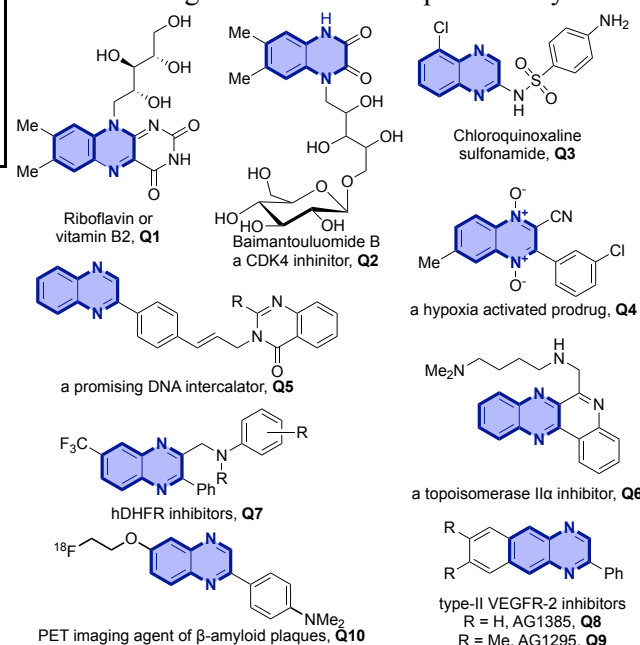


Figure 1. Important Quinoxaline Derivatives

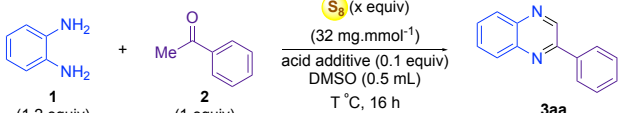
In view of high availability of alkyl aryl ketones, their use as the starting materials along with *o*-phenylenediamines as bis-nucleophiles for the

synthesis of quinoxalines is undoubtedly an attractive approach from both practical and theoretical aspects.

Cho et al have developed an aerobic oxidative coupling of ketones with *o*-phenylenediamines in PEG-400 at 60 °C under an atmosphere of air in the presence of KOH to afford the corresponding quinoxalines in good yields.^[12] However, besides long reaction time required for this transformation (40 h), the reaction did not proceed satisfactorily with acetophenone, 2-phenylquinoxaline being formed in only 20% yield. One of the explanation for this low efficiency of the aerobic conditions is the high reactivity of molecular oxygen with *o*-phenylenediamine derivatives, especially at elevated temperatures. To avoid unwanted oxidation of *o*-phenylenediamines, the ketones could be oxidized beforehand to α -hydroxyimino ketones under diazotization conditions (NaNO₂/HCl or RONO/TMSCl), followed by condensation with *o*-phenylenediamines.^[13]

During the course of our exploration of new redox chemistry of elemental sulfur S₈ applicable to the synthesis of molecules of interest,^[14] especially on large scale production, we found that while this simple substance is particularly reactive to the enolizable ketones to yield complex mixture of organosulfur derivatives, aza nucleophiles such as anilines or even *o*-phenylenediamines are relatively stable to this element, even at high temperatures. Based on these observations, we reasoned that elemental sulfur, an inexpensive but user-friendly and versatile synthetic tool, could be an excellent solution for direct oxidative coupling of alkyl aryl ketones with *o*-phenylenediamines to yields quinoxalines.

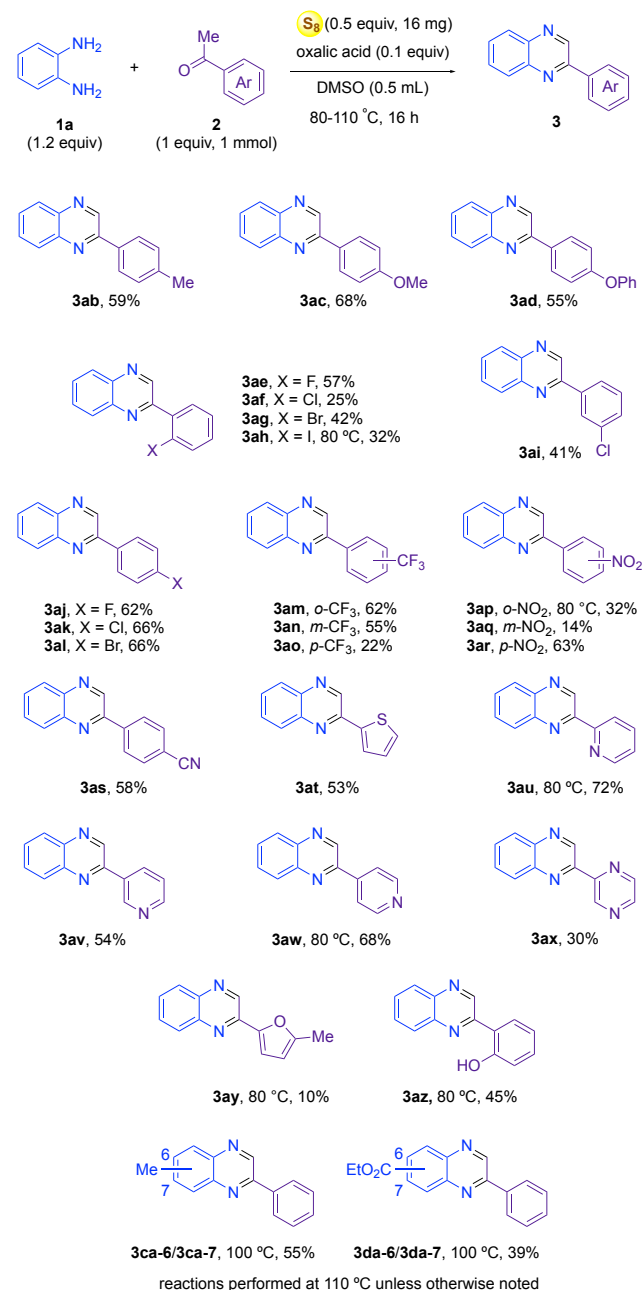
Table 1. Screening of the Reaction Conditions



Entry ^[a]	x	Acid additive	T (°C)	yield (%) ^[b]
1	1	-	100	31
2	1	oxalic acid•2H ₂ O	100	45
3	1	PTSA•H ₂ O	100	42
4	1	TFA	100	44
5	1	oxalic acid•2H ₂ O	110	65
6	1	oxalic acid•2H ₂ O	120	60
7	1	oxalic acid•2H ₂ O	90	62
8	1	oxalic acid•2H ₂ O	80	52
9	0	oxalic acid•2H ₂ O	110	0 ^[c]
10	0.2	oxalic acid•2H ₂ O	110	16
11	0.5	oxalic acid•2H₂O	110	67
12 ^[d]	0.5	oxalic acid•2H ₂ O	110	65

^[a] Reaction conditions: *o*-phenylenediamine **1a** (1.2 mmol, 130 mg, 1.2 equiv), acetophenone **2a** (1 mmol, 120 mg), sulfur (x equiv, x mmol, 32 mg/mmol), additive (0.1 mmol, 0.1 equiv) in DMSO (0.5 mL), T °C, 16 h. ^[b] Isolated yield unless otherwise noted. ^[c] Determined by ¹H NMR of the crude mixture. ^[d] Reaction performed under an argon atmosphere.

While sulfur was generally using as stoichiometric oxidant,^[15] we noticed that when the reactions were performed in DMSO, the amount of S₈ could be lowered. If sulfur does not act as a sulfur building-block, using sulfur in catalytic amounts could be beneficial by circumventing the formation of unwanted organosulfur by-products.



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

To confirm this assumption, we initiated a screening on the oxidative coupling of *o*-phenylenediamine (**1a**) with acetophenone (**2a**) and the results were listed in Table 1. Treatment of **1a** and **2a** in DMSO (0.5 mL) in the presence of S (1 eq) at 100 °C for 16 h afforded 2-phenylquinoxaline (**3aa**) in 31% isolated yield (entry 1). The presence of an acid additive such as oxalic acid dihydrate,^[16] TsOH•H₂O, TFA was found to favor the

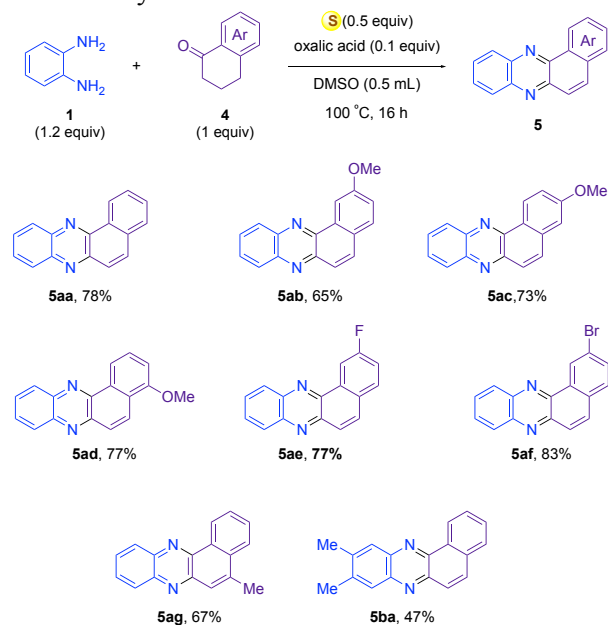
reaction by accelerating the condensation of the ketone function of **1a** with the amino groups of **2a** leading to **3aa** in 45% (entries 2-4). While the best yield was achieved at 110 °C (entry 5), the reaction performed at other temperatures resulted in lower yields of **3aa** (entries 6-8), possibly due to degradation of *o*-phenylenediamine **1a** via uncontrollable reactions with DMSO at higher temperature (entry 6) or incomplete conversion at lower temperatures (entries 7-8). The reaction was carried out in the absence of sulfur led to complex mixtures with no trace of the expected quinoxaline **3aa** (entry 9). Further variation of sulfur loading (entries 91-11) confirmed the optimal amount of sulfur was 50 mol % (entry 11).

The scope of the acetophenone substitution was next examined. As shown in Scheme 1, 2-arylquinoxalines **3** bearing a substituent of different electronic natures were accessible. Functional groups such as alkyl (**3ab**, **3ca**), ether (**3ac-3ad**), halides (F, Cl, Br, I, **3ae-3al**), CF₃ (**3am-3ao**), NO₂ (**3ap-3ar**), CN (**3as**) and ester (**3da**), as well as hetaryls (2-thienyl **3at**, pyridyls **3au-3aw**, pyrazinyl **3ax** and furyl **3ay**) were compatible with the reaction conditions. The reaction of *o*-hydroxyacetophenone proceeded in the same manner to provide the expected hydroxyquinoxaline **3az** along with a small amount of cyclized product (20%) issued from the dehydrogenation of the hydroxy group and C-3 of the quinoxaline ring. In general, the reactions could be performed at lower temperature (80 °C) for the substrates **2** having a substituent (*o*-I, *o*-OH, *o*-NO₂) or a heteroaromatic ring (2-pyridyl, 4-pyridyl, 2-furyl) likely to give side reaction. Notably, even at this lower temperature, 2- and 4-pyridyl products **3au** and **3aw** could be obtained. In these cases, even the ¹H NMR spectra of the crude mixtures showed that the expected product **3au** and **3aw** were practically the only aromatic component, the isolated yields remained 68-72%, which could be attributed to degradation of both starting materials upon heating with DMSO/S₈, leading to insoluble degradation products.

As expected, when 4-substituted *o*-phenylenediamines **1c,d** were used, the reactions led to mixtures of nearly equimolar quinoxalines **3ca-6/3ca-7** and **3da-6/3da-7**. Our preliminary results showed that the reaction with dialkyl ketones such as dipropyl and diethyl ketones led to the expected quinoxalines but the reaction mixtures were less clean and the purification was complicated.

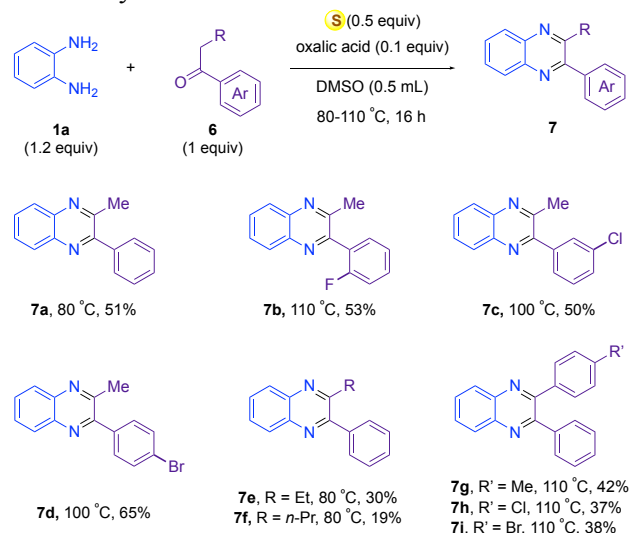
More interestingly, our protocol was applicable to the reaction of *o*-phenylenediamines **1a** with α -tetralones **4a**. At 100 °C, the fused tetracyclic products naphthoquinoxaline **5aa** was formed as a result of an additional aromatization (Scheme 2). It should be emphasized that compound **5aa** and derivatives were known for their applications as both advanced materials^[17] and bioactive molecules^[18] and their syntheses were based on elaborate substrates and multi-step process, using several solvents and reagents, under not so simple reaction and purification conditions.^[19] Furthermore, diverse methoxy-substituted as well as halogenated (F, Br) α -tetralones

displayed good reactivity affording the expected naphthoquinoxalines **5ab-5af** in good yields. 4-Methyl- α -tetralone **4g** was similarly converted to **5ag**. Finally, 4,5-dimethyl-1,2-phenylenediamine **1b** was converted to the corresponding naphthoquinoxaline **5ba** in 47% yield.



Scheme 2. Scope of the Reactions between **1** and **4**

We also briefly investigated the reactivity of aryl ketones **6** with longer alkyl chains. As depicted in Scheme 3, propiophenones **6a** as well as its derivatives bearing a halo substituent at different positions **6b-6d** reacted with *o*-phenylenediamine **1** under the standard conditions to 2-aryl-3-methylquinoxalines **7a-7d** in moderate yields.

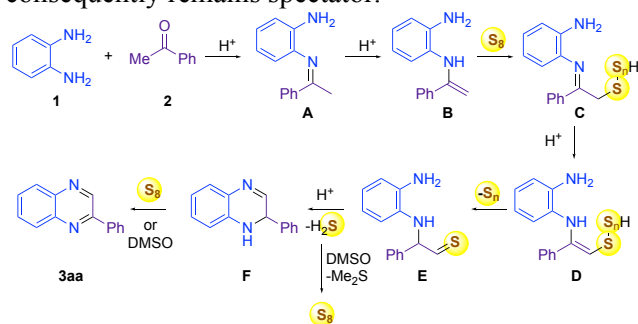


Scheme 3. Reactions of **1a** with ketones **6**

The reactions with butyrophenone **6e** and valerophenone **6f** provided the expected 3-alkylquinoxaline products **7e-7f** with decreased yields.

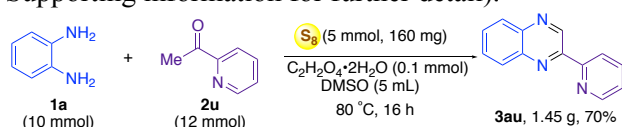
The lower yields in these cases could be attributed to the formation of 2-phenylbenzimidazole (21% and 12% respectively) issued from the extrusion of the alkyl group from ketones **6e-6f** while the benzoyl moiety is trapped by **1**. When deoxybenzoin substrates **6g-6i** were used, the oxidative condensation yielded the desired product **7g-7i** with 37-42% yields.

On the basis of the previous results,^{[15],[20],[21]} a plausible mechanism is depicted in Scheme 4. An acid-catalyzed condensation of amine **1** with ketone **2** would provide imine **A**, equilibrating with its enamine **B**. Sulfuration of enamine **B** with sulfur would give rise to polysulfane **C**, which could undergo once again imine-enamine tautomerization to **D** and desulfuration to thioaldehyde **E**. Cyclization of **E** with concomitant dehydrosulfuration would lead to dihydroquinoxaline **F**, readily aromatized to **3aa** by either sulfur or DMSO. The oxidation of H₂S by DMSO to regenerate elemental sulfur would complete the redox catalytic cycle. Due to this characteristic, free H₂S is maintained in low concentration in the reaction mixture, thus avoiding unwanted side reactions such as sulfuration and reduction in case of substrates bearing substituents capable of reacting with H₂S such as nitro, cyano as well as *o*-halo. On the other hand, dimethyl sulfide, a byproduct of regeneration of elemental sulfur from H₂S and DMSO, is relatively non-reactive and consequently remains spectator.



Scheme 4. Proposed Reaction Mechanism

Finally, to demonstrate the utility of our transformation, we set up a ten-mmol scale reaction for the synthesis of **3au** quinoxaline, which could serve as a chelating ligand (Scheme 5). The expected product could be obtained in 70% yield (1.45 g) (See Supporting information for further detail).



Scheme 5. Gram-scale Synthesis of **3au**

In summary, we have developed a practical method for the sulfur-catalyzed oxidative condensation of acetophenones **2** with *o*-phenylenediamines **1** with

DMSO a terminal oxidant for the synthesis of quinoxalines **3**. The method was also successfully extended to α -tetralones **4** to provide naphthoquinoxalines **5** as well as to propiophenones and higher homologues **6**, leading to a wide range of 3-substituted 2-arylquinoxalines **7**. This strategy possesses the advantages of inexpensive substrates and reagents under heating conditions. Considering the low cost of odorless and non-toxic elemental sulfur as well as its redox catalytic activity, we believe this seminal result will inspire further exploration and application in organic synthesis of molecules of interest.

Experimental Section

General procedure for the synthesis of quinoxalines **3**, **5** and **7**

A mixture of ketones **2**, **4** or **6** (1 mmol), *o*-phenylenediamine **1** (1.2 mmol, 1.2 equiv), sulfur (0.5 mmol, 16 mg) and oxalic acid dihydrate (13 mg, 0.1 mmol) in DMSO (0.5 mL) in a 7 mL test tube closed with a rubber septum equipped with a deflated rubber balloon was heated at 80-110 °C (see Schemes 1-3) for 16 h. The crude mixture was purified by column chromatography on silica gel (EtOAc:hexane or CH₂Cl₂: EtOAc) to provide the expected quinoxalines **3**, **5** or **7**, respectively.

Acknowledgements

We thank Vietnam Academy of Science and Technology for valuable financial support (NCVCC06.04/21-21).

References

- [1] a) T. Kaushal, G. Srivastava, A. Sharma, A. Singh Negi, *Bioorg. Med. Chem.* **2019**, *27*, 16; b) B. Borah, L. R. Chowhan, *RSC Adv.* **2021**, *11*, 37325; c) V. K. Maikhuri, Prasad, A. K. Jhab, A. S. Srivastava, *New J. Chem.* **2021**, *45*, 13214; d) T. B. Nguyen, P. Retailleau, A. Almourabit, *Org. Lett.* **2013**, *15*, 5238; e) T. B. Nguyen, L. Ermolenko, A. Almourabit, *Synthesis* **2015**, *47*, 1741; c) V. K. Maikhuri, A. K. Prasad, A. Jhab, S. Srivastava, *New J. Chem.* **2021**, *45*, 13214; d) T. B. Nguyen, P. Retailleau, A. Almourabit, *Org. Lett.* **2013**, *15*, 5238; e) T. B. Nguyen, L. Ermolenko, A. Almourabit, *Synthesis* **2015**, *47*, 1741.
- [2] a) M. Zhang, Z. C. Dai, S. S. Qian, J. Y. Liu, Y. Xiao, A. M. Lu, H. L. Zhu, J. X. Wang, Y. H. Ye, *J. Agric. Food Chem.* **2014**, *62*, 9637; b) X. H. Liu, W. Yu, L. J. Min, D. E. Wedge, C. X. Tan, J. Q. Weng, H. K. Wu, C. L. Cantrell, J. Bajsa-Hirschel, X. W. Hua, S. O. Duke, *J. Agric. Food Chem.* **2020**, *68*, 7324; c) T. P. Selby, L. R. Denes, J. J. Kilama, B. K. Smith, *ACS Symp Ser.* **1995**, *584*, 171.
- [3] a) M. R. Reddy, S.H. Han, J. Y. Lee, S. Y. Seo, *Dyes Pigm.* **2018**, *153*, 132; b) S. Kothavale, W. J. Chung, J. Y. Lee, *ACS Appl. Mater. Interfaces* **2020**, *12*, 18730; c) W. Zhang, C. Sun, S. Qin, Z. Shang, S. Li, C. Zhu, G. Yang, L. Meng, Y. Li, *ACS Appl. Mater. Interfaces* **2021**, *13*, 55403; d) L. Li, G. Zhang, B. He, S. Liu, C. Duan, F. Huang, *Mat. Chem. Front.* **2017**, *1*, 49; e) T. Wang, T. K.

- Lau, X. Lu, J. Yuan, L. Feng, L. Jiang, W. Deng, H. Peng, Y. Li, Y. Zou, *Macromolecules* **2018**, *51*, 2838; f) K. B. Woody, E. M. Henry, S. Jagtap, D. M. Collard, *Macromolecules* **2011**, *44*, 9118.
- [4] a) Y. Yang, Y. G. Xia, Q. H. Wang, D. Q. Dou, H. X. Kuang, *Fitoterapia* **2010**, *81*, 1003; b) K. Gurushankar, H. Rimac, V. Potemkin, M. Grishina, *J. Mol. Struct.* **2021**, *1230*, 129925.
- [5] H. Gao, E. F. Yamasaki, K. K. Chan, L. L. Shen, R. M. Snapka, *Cancer Res.* **2000**, *60*, 5937.
- [6] L. Chang, X. Liu, D. Wang, J. Ma, T. Zhou, Y. Chen, R. Sheng, Y. Hu, Y. Du, Q. He, B. Yang, H. Zhu, *PLoS One* **2015**, *10*, e0144506.
- [7] J. D. Palem, G. R. Alugubelli, R. Bantu, L. Nagarapu, S. Polepalli, N. Jain, R. Bathini, V. Manga, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3014.
- [8] F. Palluotto, A. Sosis, O. Pinato, G. Zoidis, M. Catto, C. Sissi, B. Gatto, A. Carotti, *Eur. J. Med. Chem.* **2016**, *123*, 704.
- [9] S. Piras, A. Carta, I. Briguglio, P. Corona, G. Paglietti, R. Luciani, M. P. Costi, S. Ferrari, *Eur. J. Med. Chem.* **2014**, *21*, 169.
- [10] M. I. Shahin, D. A. A. El Ella, N. S. Ismail, K. A. Abouzid, *Bioorg. Chem.* **2014**, *56*, 16.
- [11] M. . Yoshimura, M. Ono, K. Matsumura, H. Watanabe, H. Kimura, M. Cui, Y. Nakamoto, K. Togashi, Y. Okamoto, M. Ihara, R. Takahashi, H. Saji, *ACS Med. Chem. Lett.* **2013**, *4*, 596.
- [12] C. S. Cho, W. X. Ren, S. C. Shim, *Tetrahedron Lett.* **2007**, *48*, 4665.
- [13] K. Padmavathy, G. Nagendrappa, K. V. A. Geetha, *Tetrahedron Lett.* **2011**, *52*, 544.
- [14] a) T. B. Nguyen, *Adv. Synth. Catal.* **2020**, *362*, 3448 b) T. B. Nguyen, *Adv. Synth. Catal.* **2017**, *359*, 1066; c) T. B. Nguyen, *Asian J. Org. Chem.* **2017**, *6*, 477.
- [15] a) T. B. Nguyen, P. Retailleau, *Adv. Synth. Catal.* **2018**, *360*, 2389; b) T. B. Nguyen, L. A. Nguyen, P. Retailleau, *Org. Lett.* **2019**, *21*, 6570.
- [16] T. B. Nguyen, T. M. Nguyen, P. Retailleau, *Chem. Eur. J.* **2020**, *26*, 4682.
- [17] a) H. Cheng, Q. Guo, J. Lan, C. Ran, D. Wu, H. Zhang, *Chem. Commun.* **2022**, *58*, 1581; b) Y. Takeda, M. Okazaki, S. Minakata, *Chem. Commun.* **2014**, *50*, 10291.
- [18] a) H. Hussain, S. Specht, S. R. Sarite, M. Saefel, A. Hoerauf, B. Schulz, K. A. Krohn, *J. Med. Chem.* **2011**, *54*, 4913; b) V. F. De Andrade-Neto, M. O. F. Goulart, J. F. Da Silva Filho, M. J. Da Silva, M. D. C. F. R. Pinto, A. V. Pinto, M. G. Zalis, L. H. Carvalho, A. U. Krettli, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145.
- [19] a) S. Lou, D. Xu, D. Shen, Y. Wang, Y. Liu, Z. Xu, *Chem. Commun.* **2012**, *48*, 11993; b) M. Chang, T. Lee, R. Hsu, T. Yen, *Synthesis* **2011**, 3143. Very recently, Deng et al developed a similar reaction to synthesized **5** from oxidative coupling promoted by I₂O₅ of o-phenylenediamines **1** with β-tetralones, which are more expensive and less commercially available than the corresponding α-tetralones: S. Wang, R. Li, S. Jiang, H. Huang, W. Shao, G. Deng, *Adv. Synth. Catal.* **2022**, *364*, 1481.
- [20] a) T. B. Nguyen, L. P. A. Nguyen, T. T. T. Nguyen, *Adv. Synth. Catal.* **2019**, *361*, 1787-; b) T. T. T. Nguyen, L. A. Nguyen, Q. A. Ngo, M. Koleski, T. B. Nguyen, *Org. Chem. Front.* **2021**, *8*, 1593.
- [21] For a selected interesting result on the catalysis of elemental selenium, see: Y. Li, Y. Wang, T. Yang, Z. Lin X. Jiang, *Green Chem.* **2021**, *23*, 2986.

Sulfur-Catalyzed Oxidative Condensation of Aryl Alkyl Ketones with *o*-Phenylenediamines: Access to Quinoxalines*Adv. Synth. Catal.* **Year**, *Volume*, Page – PageLe Anh Nguyen,^{b,c} Thi Thu Tram Nguyen,^d
Quoc Anh Ngo,^{*b,c} and Thanh Binh Nguyen^{*a}