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DABCO-Catalyzed DMSO-Promoted Sulfurative 1,2-Diamination of Phenylacetylenes with Elemental Sulfur and *o*-Phenylenediamines: Access to Quinoxaline-2-thiones

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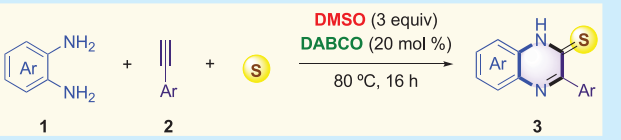
ABSTRACT: The oxidative amination of alkynes typically requires transition metal catalysts and strong oxidants. Herein, we alternatively utilize DABCO as a sulfur-activating catalyst to achieve the sulfurative 1,2-diamination of phenylacetylenes with elemental sulfur and *o*-phenylenediamines. DMSO was found to be particularly suitable for use as a terminal oxidant for this three-component process. A mechanistic study has shown that this cascade reaction is triggered by the addition of active sulfur species to the triple bond of phenylacetylenes.

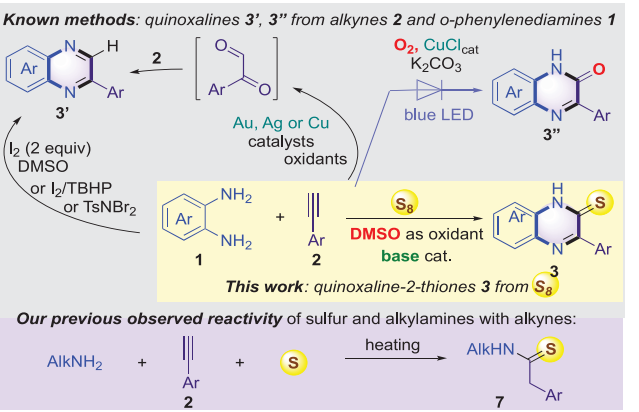


The development of new synthetic approaches to N-heterocycles from readily available starting materials is an important research area of organic synthesis. Quinoxaline is a valuable heterocyclic scaffold found in bioactive molecules[1] or functional materials (semiconductors,[2] OLEDs,[3] organic luminescent materials,[4] fluorescent dyes,[5] ionic[6] and molecular[7] recognition, and organic photovoltaics[8]). Efforts have been devoted to exploring new synthetic methodologies for the derivatization of existing quinoxalines[9] and the direct construction of quinoxaline cores. Conventionally, the latter strategy has been based on the non-redox condensation of 1,2-dicarbonyl compounds with *o*-phenylenediamines or the redox condensation of substrates with oxidation states lower than those of 1,2-dicarbonyl compounds.[10]

An attractive strategy is the direct vicinal functionalization of terminal alkynes via oxidation of the C≡C bond of alkynes to afford 1,2-dicarbonyl compounds,[11] followed by a reaction with *o*-phenylenediamines to provide 3*H*-quinoxalines **3′** (Scheme 1). Due to low reactivity of the weakly activated triple bond of phenylacetylenes with N-nucleophiles, transition metal complexes in combination with *N*-oxide oxidants {$Ph_3PAuNTf_2/O_2$,[12] $[AuCl(Ph_3P)]/AgSbF_6$/6-methoxyquinoline *N*-oxide,[13] and MCM-41-Ph_2P-$AuNTf_2$/2,3-dichloropyridine *N*-oxide}[14] have been used to catalyze the oxidation[15] of C≡C bonds.

However, in addition to the considerable cost of gold catalysts and ligands, there are two serious issues that need to be addressed: the removal of metallic residues from the products, especially for pharmaceutical applications, and the limitation of unwanted oxidation of *o*-phenylenediamines, which are particularly sensitive to conventional oxidants, including molecular oxygen.

Scheme 1. Oxidative Diamination of Alkynes 2 with Diamines 1 as an Atom Economical Strategy for Producing Quinoxalines 3



To avoid the oxidation of diamines **1**, the synthesis of quinoxalines has been carried out in two separate steps: oxidation of alkynes **2** to 1,2-dicarbonyl compounds and condensation with **1**. On the contrary, the use of halogen-based oxidative systems such as molecular iodine in stoichiometric[16a] or catalytic amounts (with TBHP as an oxidant)[16b] as well as $TsNBr_2$[17] allowed the direct oxidative

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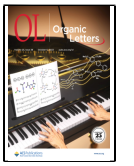

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coupling of **2** with **1** to provide **3′**. Interestingly, Hwang et al. found that in the presence of the CuCl catalyst, alkynes **2** underwent an oxygenative diamination with diamines **1** and dioxygen upon aerobic blue LED irradiation to give quinoxalin-2-ones **3″**.[18]

Since Willgerodt's seminal report[19] on the use of sulfur in organic synthesis, this substance has been proven to be a versatile and powerful tool for promoting various cascade transformations. It has provided direct access to valuable molecules, with or without sulfur, with high atom, step, and redox efficiency. Our group has previously reported an uncatalyzed reaction of alkynes with alkylamines and elemental sulfur, leading to thioamides **7** with complete atom efficiency.[20] It has also been demonstrated that when DMSO was used as an additive, the reactivity of the sulfur was significantly increased and the reaction could be performed at lower temperatures.[21] Moreover, in these cases, DMSO could act as a mild and selective oxidizing/dehydrogenating agent.[22]

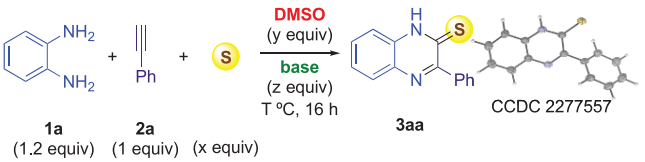
We imagined that using sulfur in place of oxygen could provide a general alternative for transition metal-catalyzed aerobic oxidative coupling involving phenylacetylenes **2** and *o*-phenylenediamines **1**. We argue that sulfur, when appropriately activated by a base and DMSO, could add to a weakly reactive triple bond and thus trigger a cascade of oxidative amination. In this way, this element would be ideal as both a sulfurating agent and a terminal oxidant for a variety of redox transformations even in the absence of a transition metal catalyst.

In this context, it is highly desirable but challenging to develop a more efficient, environmentally benign, and atom economical approach for the direct coupling of **1** with terminal **2** using sulfur as a unique sulfur building block and an inexpensive and user-friendly external oxidant in the absence of a transition metal catalyst.

To confirm our hypothesis, we set up a model reaction of **1a** with **2a** with sulfur as the sulfur source and DMSO as the oxidant (Table 1). To our delight, in the presence of a base in a stoichiometric amount such as *N*-methylpiperidine, the expected quinoxaline **3aa** was obtained in a good yield upon heating overnight at 80 °C (entry 1). Interestingly, the highly pure product was readily isolated by precipitation from the crude mixture with methanol. The quinoxaline-2-thione structure was confirmed by X-ray crystallography. Other tertiary amines with similar basicity were also efficient catalysts (entries 2−4). On the contrary, weaker bases (pyridine and 3-picoline) were inefficient (entries 5 and 6, respectively). Piperidine was not suitable to act as a catalyst as *N*-(phenylthioacetyl)piperidine was the main product, which was obtained from the addition of sulfur and piperidine to phenylacetylene (entry 7). When the reaction was performed at a lower temperature (60 °C, entry 8), the reaction was slowed considerably; the product could also be isolated by filtration in a lower yield (entry 8).

At this stage, we focused our attention on decreasing the amount of the base catalyst. When the amount of *N*-methylpiperidine was reduced, the yields decreased gradually (entries 9−11). Because DABCO, which is an easy-to-handle and free-flowing solid, has previously been shown to be an excellent catalyst for many sulfuration reactions involving sulfur, it was chosen to replace *N*-methylpiperidine when only catalytic amounts were used (entries 12 and 13) and displayed excellent performance. Finally, by varying the amounts of sulfur and DMSO (entries 13−17), we consolidated our optimized conditions (entry 12).

Table 1. Screening of the Reaction Conditions



entry[a]	S (equiv)	DMSO (equiv)	base (equiv)	*T* (°C)	yield (%)[b]
1	1.5	3	*N*-methylpiperidine (1)	80	85
2	1.5	3	NEt_3 (1)	80	78
3	1.5	3	NPr_3 (1)	80	80
4	1.5	3	DIPEA (1)	80	75
5	1.5	3	pyridine (1)	80	trace[c]
6	1.5	3	3-picoline (1)	80	trace[c]
7	1.5	3	piperidine (1)	80	35
8	1.5	3	*N*-methylpiperidine (1)	60	30
9	1.5	3	*N*-methylpiperidine (0.5)	80	75
10	1.5	3	*N*-methylpiperidine (0.2)	80	44
11	1.5	3	*N*-methylpiperidine (0.1)	80	15
12	1.5	3	DABCO (0.2)	80	87
13	1.5	3	DABCO (0.1)	80	51
14	1.5	6	DABCO (0.2)	80	32
15	1.5	2	DABCO (0.2)	80	56
16	1.0	3	DABCO (0.2)	80	65
17	2	3	DABCO (0.2)	80	86

[a]Reaction conditions: *o*-phenylenediamine **1a** (1 equiv, 1 mmol, 108 mg), phenylacetylene **2a** (1.2 equiv, 1.2 mmol, 122 mg), sulfur (*x* equiv, 32 mg $mmol^{-1}$), base (*z* equiv) in DMSO (0.2 mL, 3 equiv, 3 mmol). [b]Yield of **3aa** isolated by column chromatography. [c]Determined by ^1H NMR of the crude reaction mixture.

With the optimized conditions in hand (entry 12, Table 1), the scope of the oxidative sulfurative diamination of phenylacetylenes was investigated, as outlined in Scheme 2. Numerous phenylacetylenes bearing electron-donating and electron-withdrawing substituents reacted with unsubstituted *o*-phenylenediamine **1a** to afford products in 51−96% yields on the 1 mmol scale. These substituents could be located at the *ortho*, *meta*, or *para* position of the phenyl ring of the acetylene substrates.

The mild conditions allowed for high chemoselectivity. For example, functional groups such as alkoxy (**3ae−3ag**, aromatic ring sulfuration) and cyano (**3ao**, hydrosulfuration with H_2S) are well tolerated. Synthetically relevant functionalities, including F, Cl, and Br (**3ah−3ak**), are also compatible.

The structure of **3al** has been unambiguously confirmed by X-ray chromatography. 3-Ethynylpyridine **2p**, a heterocyclic derivative of phenylacetylene, was found to be a competent substrate, leading to quinoxaline **3ap** in good yield. Similarly, we extended the scope to 4,5-dimethyl-*o*-phenylenediamine **1b**, which was found to react in the same manner to afford quinoxalines **3bc−3bo**.

When unsymmetrical *o*-phenylenediamines (**1c−1e**) bearing an alkyl substituent such as a 4-methyl or 3-methyl group were allowed to react with phenylacetylene **2a**, the expected quinoxalines **3ca** and **3de** were formed in good yields as

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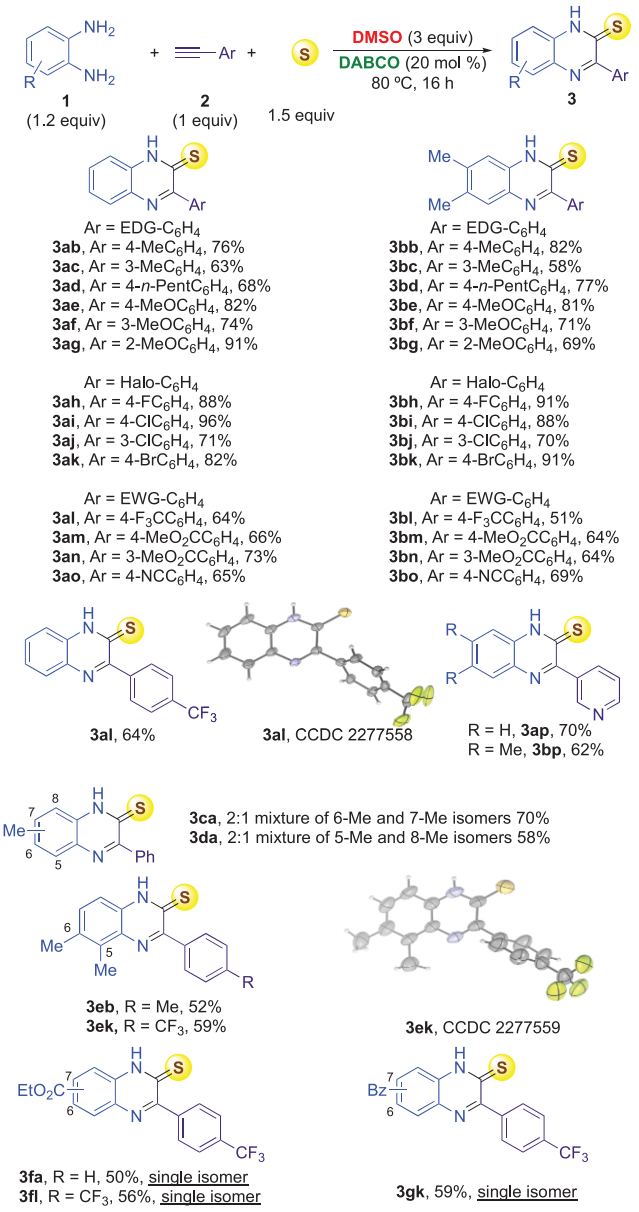
Scheme 2. Oxidative Sulfurative Diamination of Alkynes 2

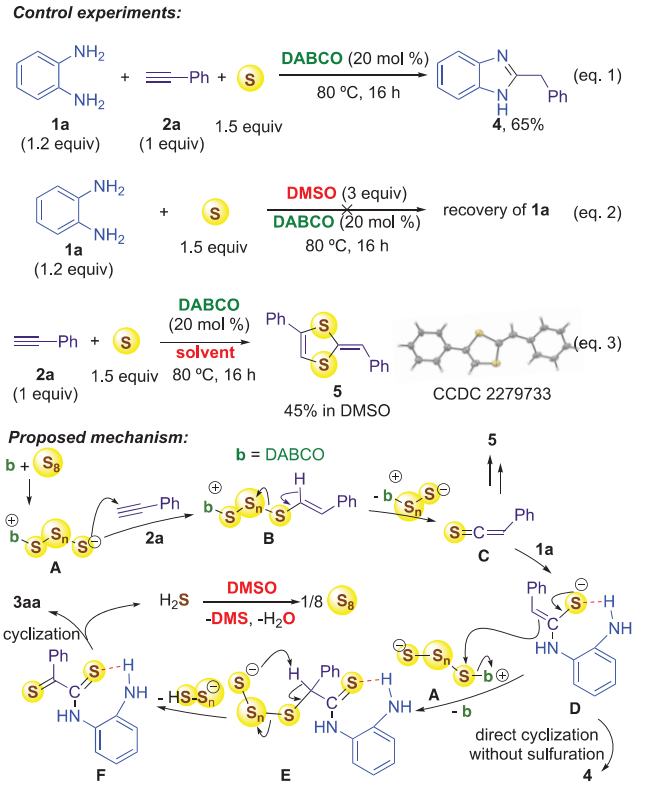


approximately 2:1 mixtures of two possible regioisomers. On the contrary, *o*-phenylenediamines bearing two methyl groups at positions 3 and 4 (3,4-dimethyl-*o*-phenylenediamine **1e**) or an EWG at position 4 such as carboxylate esters (**1f** and **1g**) or benzoyl (**1h**) resulted in only one regioisomer (**3eb**, **3ek**, **3fa**, **3gl**, and **3hk**). Only the structure of **3ek** was confirmed by X-ray crystallography, showing a *syn* configuration between the two methyl groups and the *p*-(trifluoromethyl)phenyl one.

However, aliphatic acetylenes (cyclohexylacetylene and 1-octyne), 1-phenylpropyne, and diphenylacetylene failed to react under the conditions developed, probably due to either lower polarizability or higher steric hindrance of their triple bond.

To understand the reaction mechanism, we conducted several experiments (Scheme 3). First, in the absence of DMSO as an oxidant, the reaction of **1a** with **2a** led to benzimidazole **4** as previously observed for aliphatic amines (eq 1, Scheme 3).[20] This result highlights the importance of DMSO as a specific oxidant for the formation of quinoxaline

Scheme 3. Control Experiment and Proposed Mechanism



3aa. While **1a** was found to be stable, remaining unchanged in the absence of **2a** (eq 2, Scheme 3), alkyne **2a** underwent sulfurative dimerization to afford 1,3-dithiole **5** when heated with sulfur and DABCO (eq 3, Scheme 3). This dimerization of **2a** occurred even without DMSO or in other solvents (*N*-methylpyrrolidin-2-one and pyridine). An additional control experiment to compare the reactivity between phenylacetylene **2a** and its synthetic equivalent acetophenone **8** (see the Supporting Information) reveals that in case of **2a**, the key initial step is an addition of a sulfur species to the triple bond, while in the case of **8**, the first step is C═N bond formation via imine condensation of **8** with an amino group of **1a**.

On the basis of these results, we propose a plausible mechanism for alkyne **2a** that starts with the addition of highly nucleophilic polysulfide **A**, formed from ring opening of S_8 by DABCO, to the triple bond of **2a** to give polysulfide **B**. Fragmentation of **B** would lead to thioketene **C**. In the absence of an N-nucleophile, **C** is dimerized into 1,3-dithiole **5**. On the contrary, **C** reacted with *o*-phenylenediamine **1a** to form ene-thiolate **D**, stabilized by the intramolecular H-bonding between the thiolate and the free *o*-NH_2 group. Such H-bonding is not present if aniline is used in place of *o*-phenylenediamine **1a**, which is in agreement with the stability of thioamide **7a** to the oxidation into oxo thioamide **9** by DMSO as mentioned in eq 4a. The stabilization of ene-thiolate **D** by an intramolecular H-bond would facilitate its further oxidation to thione thioamide **F** by **A** via polysulfide **E**. Cyclization of **F** would yield **3aa**. The role of DMSO is to regenerate sulfur from H_2S formed throughout the process and to favor the oxidation of **D** to **F** by enhancing the oxidizing reactivity of **A** instead of the cyclization of **D** to **4** without any additional oxidation.

Finally, to complete this study, we present some interesting results (Scheme 4). First, when *o*-bromophenylacetylene **10** as an alkyne substrate was allowed to react with *o*-phenylenedi-

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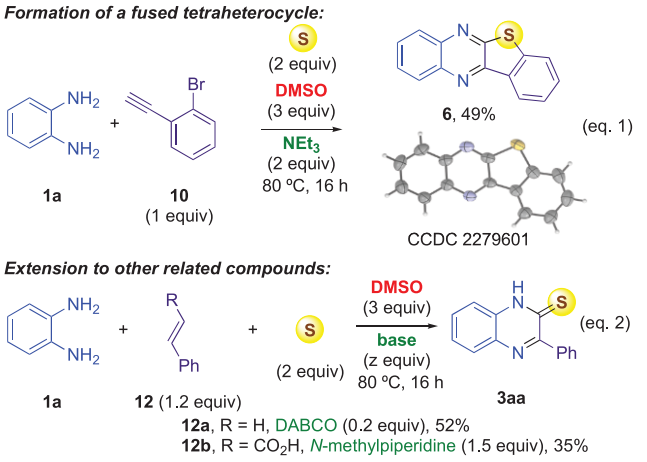
Scheme 4. Synthetic Variation



amine **1a** using 2 equiv of triethylamine as a base, fused tetraheterocyclic compound **6** was obtained in moderate yield (eq 1, Scheme 4). Second, we found that some derivatives of phenylacetylene such as its lower-oxidation state derivative styrene **12a** or cinnamic acid **12b** displayed similar reactivity, with an initial step of addition of a sulfur species to their olefinic bonds (eq 1, Scheme 4). Both **12a** and **12b** reacted with **1a** under slightly modified conditions to afford **3aa**. These results open new avenues for the synthesis of quinoxalines as well as their fused derivatives with a flexible choice of starting materials.

In summary, we developed a strategy for the direct vicinal functionalization of phenylacetylenes **2** with *o*-phenylenediamines **1** using elemental sulfur. This metal-free reaction exploits the unique activation of sulfur in DMSO in the presence of DABCO as a basic catalyst to provide quinoxaline-2-thiones **3**. Importantly, an investigation of the scope of this reaction indicates that this concept can be applied to diverse phenylacetylenes and nucleophilic *o*-phenylenediamine coupling partners, leading to the expected products in high yields with easy purification by simple filtration in most cases. This methodology could therefore be a powerful addition to the toolbox of quinoxaline synthesis, as either final products or intermediates for further functionalization.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02835.

Experimental procedures; characterizations of compounds **3**−**6**, **7a**, and **9**; and copies of their NMR spectra and crystal data (PDF)

Accession Codes

CCDC 2277557−2277559, 2279601, and 2279733 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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