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One-Pot Regiospecific Synthesis of Quinoxalines via a CH_2-Extrusion Reaction

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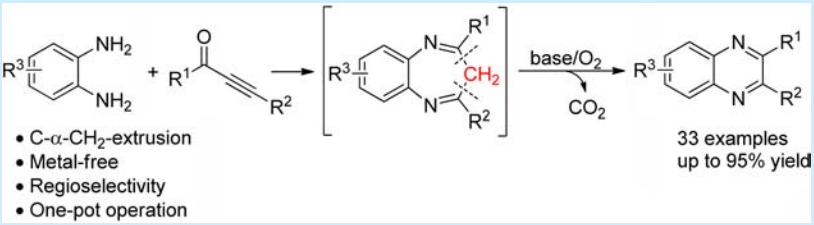
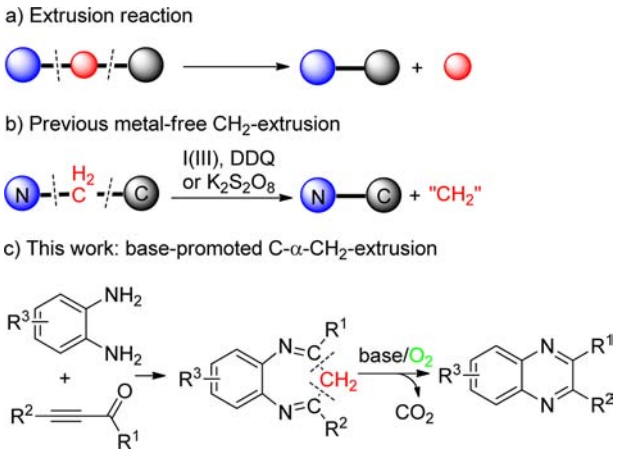
Supporting Information



ABSTRACT: A convenient "one-pot" regiospecific synthesis of substituted quinoxalines from *o*-phenylenediamines and ynones under metal-free conditions has been developed. An intermolecular Michael addition reaction, a dehydration condensation, and a base-promoted C-α-CH_2-extrusion were involved in this procedure, which features high regioselectivity, efficiency, and environmental friendliness. Various quinoxalines were provided in up to 95% yield for 33 examples.

An extrusion reaction, which is the reverse of the insertion reaction, involves the removal of an atom or a group from a given combination of functional groups and the reformation of a new bond between the atoms to which the departing moiety was attached (Scheme 1a).[1] Transition-metal-catalyzed decarboxylation and decarbonylation reactions are representative examples, in which carbon dioxide and carbon monoxide are extruded from substrates, respectively.[2] However, with more classical organic substrates, reports on the CH_2-extrusions are rare, especially under transition-metal-free conditions (Scheme 1b).[3] In 2013, the Zhu group presented a hypervalent iodine(III)-promoted tandem demethylenation/C−H cycloamination of *N*-benzyl-2-aminopyridines via C−C and C−N bonds cleavage.[3b] In 2014, the Laha group developed a novel conversion of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines to phenazines through $K_2S_2O_8$-mediated tandem oxidative removal of a benzylic methylene.[3d] Recently, Lacour and coworkers reported a DDQ-promoted CH_2-extrusion reaction for the enantiospecific synthesis of Tröger bases.[3e] Notably, these transition-metal-free CH_2-extrusion reactions are limited to the cleavage of a CH_2−N bond and a CH_2−C bond. Simultaneous cleavage of two CH_2−C bonds and generation of a new C−C bond remain unprecedented.

Scheme 1. Extrusion Reaction



On the other hand, quinoxaline is an important class of N-heterocycles and well-known for their wide range of biological activities.[4] This scaffold is also an active ingredient of some antitumor agents[5] and widely exists in natural products[6] and advanced functional materials.[7] Conventional approaches to quinoxalines involve the Lewis/Brønsted acid or Lewis base promoted reaction of *o*-phenylenediamine with a 1,2-diketone or its analogues.[8] However, these methods suffer from poor regioselectivity when asymmetrical *o*-phenylenediamines and 1,2-diketones are used. In our continuing interest in ynone-based heterocycle synthesis,[9] we develop a novel base-promoted C-α-CH_2-extrusion reaction of benzo[*b*][1,4]-diazepines for the regiospecific synthesis of quinoxalines, in which two CH_2−C bonds were simultaneously cleaved and environmentally benign O_2 was used as the sole oxidant (Scheme 1c). This protocol features high regioselectivity, efficiency, and environmental friendliness.

We employed 2,4-diphenyl-3*H*-benzo[*b*][1,4]diazepine **1aa** as a model substrate to begin our exploration of the reaction conditions. To our delight, the desired product **2aa** was

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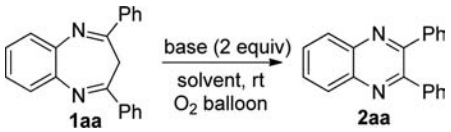
successfully obtained in a 61% yield in the DMSO/NaOH system for 3 h (entry 1). Acceptable yields were achieved in the presence of other strong bases, such as KOH, LiOtBu, NaOMe, and KOtBu (entries 2−5). The combination of KOtBu/DMSO was found to be the most effective, affording **2aa** in a 92% yield (entry 5). In contrast, benzo[*b*][1,4]diazepine **1aa** remained unreactive when weak bases, such as K_2CO_3 and Et_3N, were used (entries 6−7). The effect of the solvent was subsequently investigated, and DMSO turned out to be the best (entries 5, 8−12). When the loading of KOtBu was decreased to 1 equiv, the yield of the product was decreased to 78% (entry 13). Remarkably, a respectable 88% yield of **2aa** was achieved when the reaction was carried out in air (entry 14). However, under a N_2 atmosphere, no reaction occurred (entry 15), indicating O_2 was crucial for this transformation. Finally, the standard reaction conditions for the base-promoted synthesis of the quinoxaline derivatives were identified as follows: 2 equiv of KOtBu as the additive and DMSO as the solvent under an oxygen atmosphere.

Table 1. Optimization of Reaction Conditions[a]

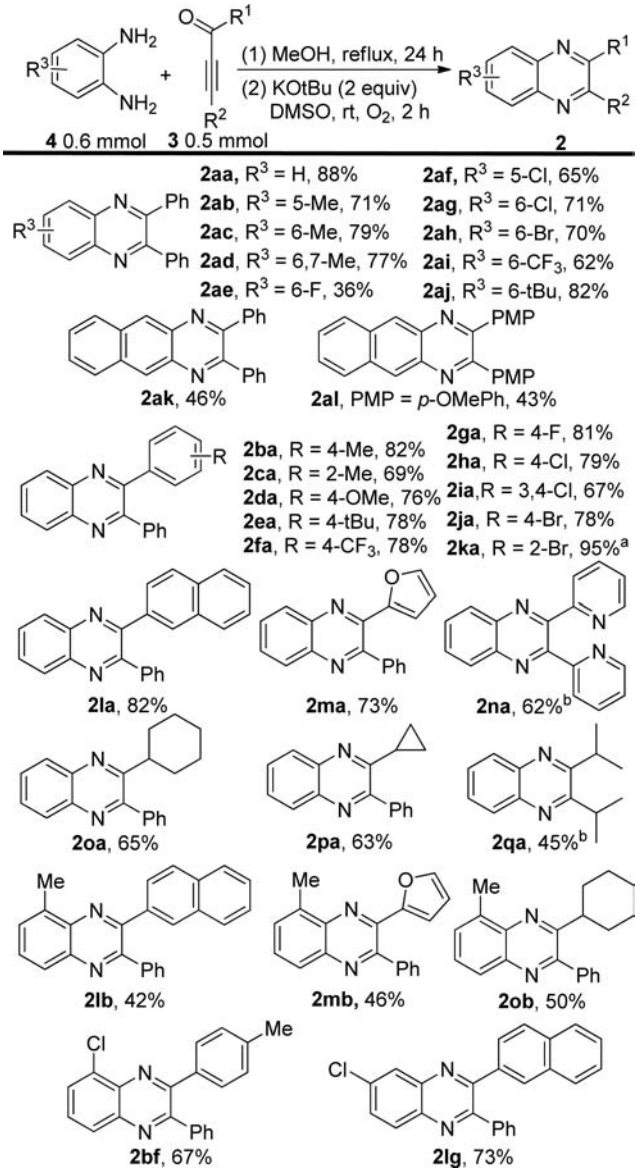


entry	base	solvent	*t* (h)	yield (%)[b]
1	NaOH	DMSO	3	61
2	KOH	DMSO	2	86
3	LiOtBu	DMSO	5	55
4	NaOMe	DMSO	3	68
5	**KOtBu**	**DMSO**	**2**	**92(91)**
6	K_2CO_3	DMSO	12	N.R.
7	Et_3N	DMSO	12	N.R.
8	KOtBu	DMF	5	63
9	KOtBu	NMP	3	88
10	KOtBu	EtOH	12	N.R.
11	KOtBu	THF	12	N.R.
12	KOtBu	toluene	12	N.R.
13[c]	KOtBu	DMSO	12	78
14[d]	KOtBu	DMSO	3	88
15[e]	KOtBu	DMSO	12	N.R.

[a]Reaction conditions: **1aa** (0.2 mmol), base (0.4 mmol), in 2 mL solvent under O_2 atmosphere. [b]Yields were determined by GC, isolated yield in brackets. N.R. = No Reaction. [c]0.2 mmol base was used. [d]Under air atmosphere. [e]Under N_2 atmosphere. DMF = *N*,*N*-dimethylformamide. DMSO = dimethyl sulfoxide. NMP = *N*-methyl-2-pyrrolidone. THF = tetrahydrofuran.

Since benzo[*b*][1,4]diazepines **1** could be readily and regiospecially prepared from ynones **3** and *o*-phenylenediamines **4** via Michael addition and dehydration−condensation,[10] a straightforward "one-pot" strategy was adopted to directly synthesize the polysubstituted quinoxaline **2** from ynones **3** and *o*-phenylenediamines **4**, avoiding isolation of the benzo[*b*][1,4]diazepine intermediates **1** (Scheme 2). To our delight, 2,3-diphenylquinoxaline **2aa** was obtained from this one-pot strategy in a similar isolated yield to that from benzo[*b*][1,4]diazepine **1aa** (88% vs 91%). Then, the scope of *o*-phenylenediamines was explored. A variety of substituted *o*-phenylenediamines with electron-donating and -withdrawing groups in the arene were subjected to our protocol. The corresponding quinoxalines were obtained in good yields for

Scheme 2. Substrate Scope



[a]Direct from benzo[*b*][1,4]diazepine substrate. [b]Using 1,3-diketone instead of ynone.

most cases (Scheme 2, **2ab**−**2aj**). The steric effects of the substitutents are not significant. Quinoxalines with 5-substitutents were obtained in similar yields to those with 6-substituents (**2ab** vs **2ac**, **2af** vs **2ag**). Halogens, including F, Cl, and Br, were all well-tolerated (**2ae**−**2ah**), which makes this reaction particularly attractive for further transformation by plenty of transition-metal-catalyzed coupling reactions. Moreover, naphthalene-2,3-diamine was also a suitable substrate, although it gave the corresponding quinoxalines in lower yields (**2ak**−**2al**).

The scope of ynones **3** was investigated as well. When R^1 and R^2 were aryl groups, 1,3-driarylynones **3** with both electron-withdrawing and -donating groups, as well as a halogen, such as methyl, methoxy, fluoro, chloro, and bromo, afforded the corresponding quinoxalines in appreciable yields (**2ba**−**2ka**). The fused aryl and heteroaryl groups, such as naphthyl, furanyl, and pyridyl, were also suitable substrates and provided the corresponding quinoxalines in 62−82% yields (**2la**−**2na**). Alkyl

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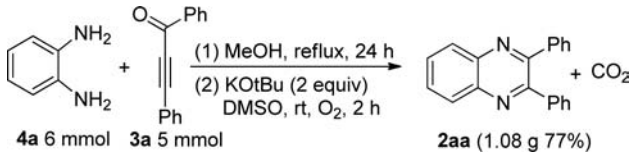
ynones also worked, giving alkyl quinoxalines in 45−65% yields (**2oa**−**2qa**). In previous 1,2-diketone-based quinoxalines synthesis,[8] asymmetrical *o*-phenylenediamines and asymmetrical 1,2-diketones delivered two regioisomers with low regioselectivity. In this strategy, when asymmetrical *o*-phenylenediamines work with asymmetrical ynones ($R^1 \neq R^2$), the desired quinoxalines were provided in moderate to good yields with excellent regioselectivity (>20:1, **2lb**−**2lg**).

To prove the practicality of this "one-pot" strategy, a gram-scale synthesis of 2,3-diphenylquinoxaline **2aa** was performed. As shown in Scheme 3, when 1.03 g of 1,3-diphenylprop-2-yn-

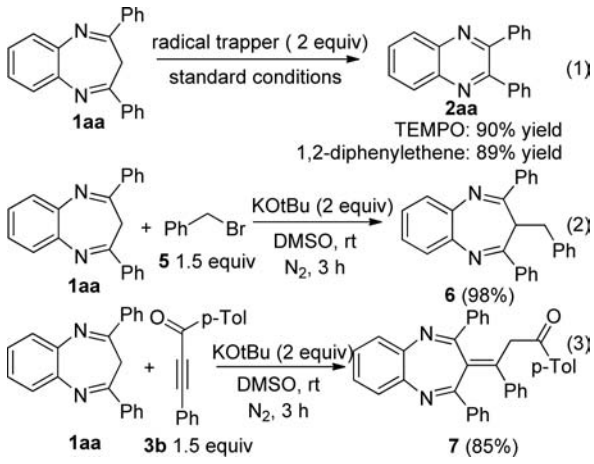
Scheme 3. Gram-Scale Synthesis of 2,3-Diphenylquinoxaline 2aa



1-one **3a** and 0.65 g of *o*-phenylenediamine **4a** were loaded, 1.08 g of diphenylquinoxaline **2aa** was obtained (77% yield). In addition, CO_2 proved to be generated by passing the gas in the reaction tube to clear limewater which turned cloudy during the test.

To gain further insight into the possible reaction mechanism, some controlled experiments were carried out. The radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidine, 1-oxy) and 1,1-diphenylethylene, did not inhibit this transformation (Scheme 4, eq 1), indicating that a radical pathway might not

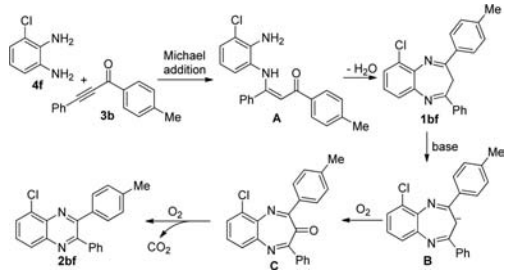
Scheme 4. Control Experiments



be involved in this reaction. On the other hand, when benzo[*b*][1,4]diazepine **1aa** reacted with 1.5 equiv of electrophiles ((bromomethyl)benzene **5**) under a N_2 atmosphere, 3-benzyl-2,4-diphenyl-3*H*-benzo[*b*][1,4]diazepine **6** was formed in a 98% yield via the S_N2 attack (eq 2). Moreover, when benzo[*b*][1,4]diazepine **1aa** was treated with ynone **3b**, a novel 3-lene-benzo[*b*][1,4]diazepine **7** was obtained from the base-promoted Michael addition and an alkene rearrangement. These results suggested that this KOtBu mediated reaction might be an anion-initiated reaction to the target products.

On the basis of the reported literature[11,9e] and aforementioned observations, a tentative reaction mechanism for this "one-pot" regiospecific synthesis of quinoxalines **2** was proposed, as depicted in Scheme 5 (**2bf** for example). Due to the steric effect, the initial Michael addition reaction of ynone

Scheme 5. Proposed Reaction Mechanism



3b and *o*-phenylenediamine **4f** regioselectively provided the enaminone **A**, followed by dehydration−condensation to give benzo[*b*][1,4]diazepine **1bf**. Deprotonation of **1bf** by KOtBu generated the anion intermediate **B**, which could be oxidized to benzo[*b*][1,4]diazepin-3-one **C** by O_2. The final quinoxaline product **2bf** was formed spontaneously by decarbonylation of **C** under O_2.[12]

In conclusion, an efficient "one-pot" approach to substituted quinoxalines in moderate to excellent yields from readily available *o*-phenylenediamines and ynones has been developed. A novel C-α-CH_2-extrusion reaction of benzo[*b*][1,4]diazepine was applied in this reaction. This protocol only required 2 equiv of KOtBu as a base, used environmentally benign O_2 as an oxidant, and generated 1 equiv of H_2O and 1 equiv of CO_2 as byproducts, which made this process environmentally friendly. Moreover, regiospecific synthesis of quinoxalines was achieved when asymmetrical *o*-phenylenediamines and asymmetrical ynones were employed, which serves as a complement to previous 1,2-diketone-based quinoxaline syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00309.

Experimental procedures, compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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