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Synthesis of the dibenzo[*b*,*d*]azepine skeleton *via* a catalyst-free ring expansion domino reaction†

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In this article, a hitherto unreported catalyst-free ring expansion reaction of tetrahydroisoquinolines with *o*-alkynylarylaldehydes for the construction of the dibenzo[*b*,*d*]azepine skeleton is described. Using air as a "green" oxidant, some important biologically active dibenzo[*b*,*d*]azepines were produced with favorable functional group tolerance and a wide substrate scope. The synthetic potential was further confirmed by facile scale-up reactions and the synthesis of isoindoline derivatives.

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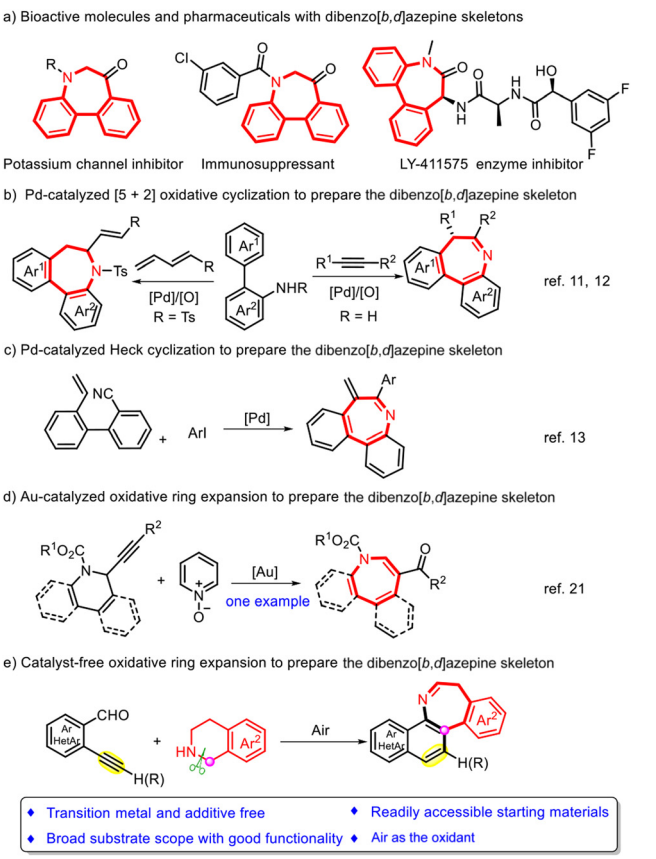
Introduction

Dibenzoazepines, a particularly valuable class of seven-membered N-heterocycles, frequently occur in many bioactive molecules, pharmaceuticals, and natural products.[1–3] Among these compounds, dibenzo[*b*,*d*]azepines have attracted most attention since they exhibit an extensive range of important bioactivities, serving as, *e.g.*, potassium channel inhibitors, enzyme inhibitors, immunosuppressants, and anticancer agents (Scheme 1a).[4–7] Due to the high benefit of dibenzo[*b*,*d*]azepine derivatives, various strategies have been developed over the last decades to synthesize such compounds.[8–10] In 2015 and 2017, Luan and co-workers reported a Pd-mediated [5 + 2] oxidative cyclization of biphenyl-2-amines with alkynes and dienes to prepare the dibenzo[*b*,*d*]azepine skeleton (Scheme 1b).[11,12] In 2022, Zhu and co-workers disclosed a different approach based on the Pd-catalyzed Heck reaction of 2-isocyano-2′-vinyl-1,1′-biphenyl with various aryl iodides to obtain the same skeleton (Scheme 1c).[13] In recent years, ring expansions emerged as some of the most attractive chemical conversions from an atom- and step-economic perspective to synthesize a versatile range of heterocyclic cores.[14,15] To date, many remarkable advancements using transition metals (*e.g.*, Ir, Rh, and Pd) have been achieved in this field,[16,17] and the most recent work has been concentrated on strained-ring systems such as three- and four-membered rings (*e.g.* cyclopropanes, cyclobutanes, aziridines, and oxiranes).[18–20] The ring expansion of six-membered rings has been less explored and only one example has been reported for the synthesis of the



Scheme 1 Synthetic strategies for dibenzo[*b*,*d*]azepine derivatives.

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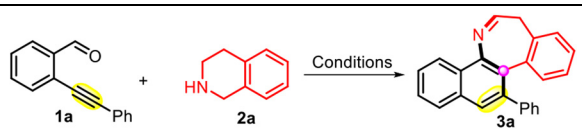
dibenzo[*b*,*d*]azepine skeleton (Scheme 1d).[21] Despite these achievements, the development of straightforward and efficient methods for constructing the dibenzo[*b*,*d*]azepine skeleton from readily accessible substrates without the use of transition metals or additives is still in its early stages. Therefore, we investigated a hitherto unreported catalyst-free ring expansion reaction of tetrahydroisoquinolines[22–25] for the construction of the dibenzo[*b*,*d*]azepine skeleton.

Results and discussion

Recently, our group completed the syntheses of a series of heterocyclic compounds.[26–30] Due to our ongoing research interest in this area, reaction screening was conducted with 2-(phenylethynyl)benzaldehyde **1a** and 1,2,3,4-tetrahydroisoquinoline (THIQ) **2a** as the model substrates to identify the suitable reaction conditions, and the results are provided in Table 1. First, the product yields were determined for various solvents under an air atmosphere after a reaction time of 4 h. Toluene exhibited the best performance with an 81% yield of the anticipated product **3a**, while the application of the other investigated solvents resulted in significantly lower yields or no reaction (entries 1–10). Control experiments revealed that no desired product was formed when the reaction was performed under N_2, implying that the presence of an oxidant was essential for this transformation (entry 11). Then, apart from air, various oxidants were screened. When the reaction was performed under an O_2 atmosphere, the obtained yield (entry 12) was similar to that observed under an air atmosphere (entry 9), indicating that the use of pure O_2 was not required for the reaction to proceed. The addition of other oxidants such as KIO_3, di-*tert*-butyl peroxide (DTBP), and MnO_2 did not further benefit the reaction (entries 13–15). Furthermore, we attempted to increase the yield of the reaction using various additives including bases ($NaHCO_3$ and K_2CO_3), Lewis acid ($AlCl_3$), iodine source (*n*-Bu_4NI), and metal catalysts ($(Ph_3P)_2PdCl_2$, $NiCl_2$, and $Cu(OAc)_2$), but none of these investigated additives exhibited the desired effect (entries 16–22). Subsequent examination of the effect of temperature revealed that inferior yields of **3a** were obtained when the temperature was reduced to rt, 80 °C, 90 °C or increased to 110 °C (entries 23–26). The effect of reaction time was also investigated, but no improvement was achieved when performing the reaction for 8 h instead of 4 h (entry 27). Therefore, the parameters used in entry 9 of Table 1 were identified as the optimized conditions.

Table 1 Optimization of the reaction conditions[a]



Entry[a]	Oxidant (equiv.)	Additive (1 equiv.)	Solvent (2 mL)	Temperature (°C)	Yield[b] (%)
1	Air	—	1,4-Dioxane	100	0
2	Air	—	DMSO	100	0
3	Air	—	DMF	100	48
4	Air	—	NMP	100	0
5	Air	—	DME	100	0
6	Air	—	MeCN	80	0
7	Air	—	Dichloroethane	80	0
8	Air	—	Xylenes	100	67
9	Air	—	Toluene	100	81
10	Air	—	THF	Reflux	0
11[c]	None	—	Toluene	100	0
12	O_2	—	Toluene	100	78
13	KIO_3 (2)	—	Toluene	100	65
14	DTBP (2)	—	Toluene	100	73
15	MnO_2 (2)	—	Toluene	100	46
16	Air	$NaHCO_3$	Toluene	100	58
17	Air	K_2CO_3	Toluene	100	0
18	Air	$AlCl_3$	Toluene	100	Trace
19	Air	*n*-Bu_4NI	Toluene	100	38
20	Air	$(Ph_3P)_2PdCl_2$	Toluene	100	71
21	Air	$NiCl_2$	Toluene	100	32
22	Air	$Cu(OAc)_2$	Toluene	100	69
23	Air	—	Toluene	rt	0
24	Air	—	Toluene	80	35
25	Air	—	Toluene	90	71
26	Air	—	Toluene	110	63
27[d]	Air	—	Toluene	100	76

[a] Reaction conditions: **1a** (0.4 mmol, 2 equiv.), **2a** (0.2 mmol), solvent (1 mL), air atmosphere, 4 h. [b] Isolated yield. [c] Under N_2. [d] Reaction time: 8 h.

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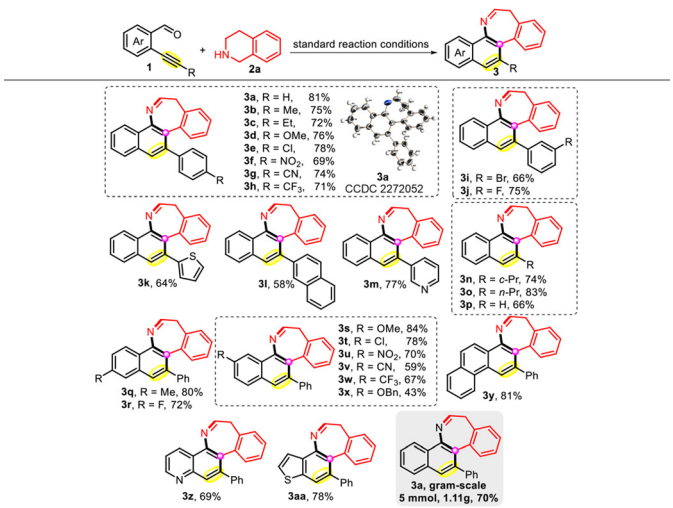
Based on the above-established optimal conditions, the scope and generality of this reaction were evaluated by examining various functionalized *o*-alkynylarylaldehydes, and the results are listed in Table 2. Generally, the electronic effect on the aromatic ring directly bonded to alkyne had no significant impact on reactivity. Substrates with various functional groups containing electron-donating or electron-withdrawing groups (Me, Et, OMe, Cl, Br, NO_2, CN, and CF_3) could easily undergo the ring expansion reaction to form the corresponding tricyclic compounds **3b–3j** in good yields. The stability of halogen substituents provides the possibility for downstream manipulations such as transition metal-mediated coupling reactions. The configuration of **3a** was verified by single-crystal X-ray diffraction analysis (CCDC 2272052†). The reaction was also viable with heteroaryl and polycyclic substituents on the triple bond, delivering the compounds **3k–3m** in 58–77% yields.

Notably, 2-formylphenylacetylene and aliphatic terminal alkynes bearing cyclopropyl and *n*-propyl groups also appeared to be suitable reactants, providing the corresponding products **3n–3p** in good yields. Subsequently, the influence of substituents on the benzaldehyde core was investigated. A range of substrates with various substituents at the 4- and 5-positions of the benzaldehyde moiety were compatible under the standard reaction conditions, delivering the target products in acceptable yields. The synthesis of polycyclic arene-/heteroarene-fused azepine derivatives from the corresponding 1-(phenylethynyl)-2-naphthaldehyde (**3y**), 2-(phenylethynyl)-3-pyridylaldehyde (**3z**), and 2-(phenylethynyl)-3-thenaldehyde (**3aa**) could also be achieved. To assess the scalability of this ring expansion reaction, a scale-up reaction was conducted, and we found that the protocol could be readily scaled up from 0.2 to 5.0 mmol with minimal yield reduction (**3a**, 70% *vs.* 81%).

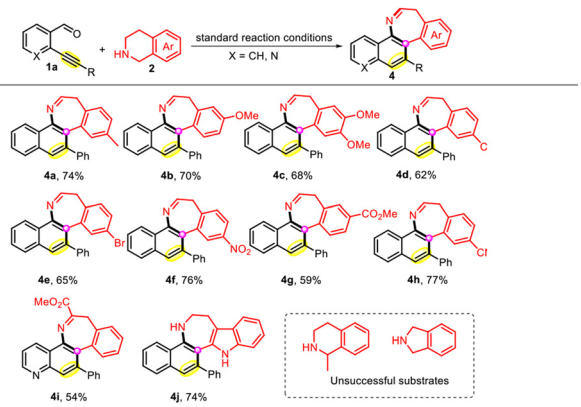
Then, the scope of the THIQ substrate was examined (Table 3). The introduction of diverse substituents, such as

Table 2 Substrate scope of *o*-alkynylarylaldehydes[a,b]



[a] Standard reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), and toluene (1 mL) in air at 100 °C for 4 h. [b] Isolated yield.

Table 3 Substrate scope of THIQs[a,b]

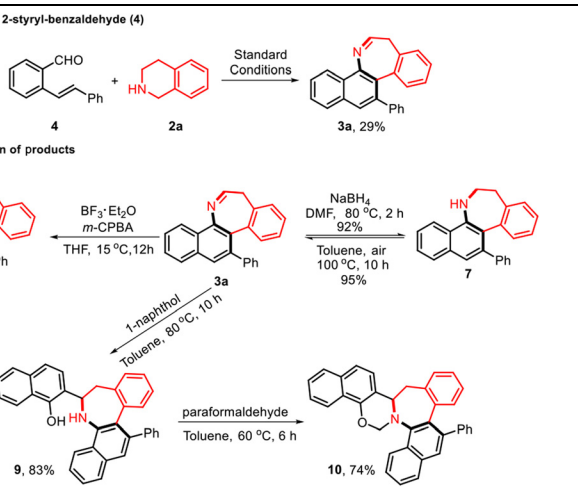


[a] Standard reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), and toluene (1 mL) in air at 100 °C for 4 h. [b] Isolated yield.

Me, OMe, Cl, Br, NO_2, CO_2Me, and CN, at the 3-, 6-, and 7-positions of the benzene ring was more compatible with this transformation, and the expected compounds **4a–4i** were obtained in good yields (54–77%). In particular, when tetrahydro-β-carboline was employed, the unoxidized azepine derivative **4j** was produced instead. Finally, the reaction of 1-methyl-THIQ and isoindoline with **1a** was investigated; however, the desired product failed to generate under optimal conditions.

Encouraged by the successful results, we wondered whether 2-styrylbenzaldehyde (**4**) (Table 4) and 2-cyanobenzaldehyde (**5**) (ESI Fig. S3†) would undergo similar efficient ring expansion reactions to provide other valuable azepine derivatives under the same conditions. **3a** could also be obtained when **4** was employed instead of **1a**. However, the reaction of **5** with THIQ compounds produced a series of 3-amino-1-isoindoline derivatives (**6a–6d**) (see the ESI for details, Fig. S3†). To demonstrate the efficacy of this method, further transformations to dibenzo[*b*,*d*]azepine products were pursued. **3a** could be converted

Table 4 Further transformations



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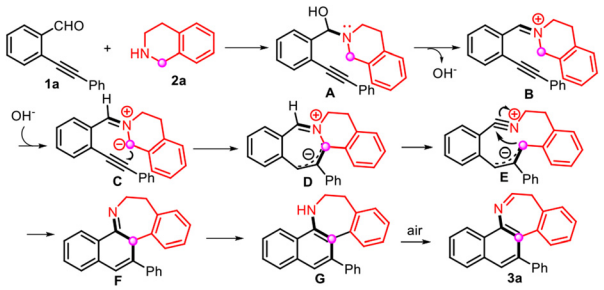

Scheme 2 Proposed mechanism.

into **7** and **8** in 92% and 86% isolated yields, respectively. Furthermore, the reaction of 1-naphthol with **3a** resulted in the bifunctional aminonaphthol **9** in 83% yield. The ring closure of **9** with a solution of HCHO as the cyclizing agent afforded a new oxazine derivative **10** in 74% yield.

Based on previous reports[31–33] and our control experiments (see the ESI for details, Fig. S1 and S2†), a feasible mechanism of the ring expansion reaction is outlined in Scheme 2. Initially, the addition of THIQ (**2a**) to *o*-alkynylarylaldehyde (**1a**) to form *N*,*O*-acetal species **A** is followed by the elimination of the hydroxide ion to afford iminium **B**. Then, **B** is deprotonated and subsequent electrocyclic ring closure generates intermediate **D**. The ring opening of **D** yields the allyl anion species **E**. Finally, the nucleophilic addition of the allyl anion species to the nitrile function, followed by aromatization and oxidation by air, furnishes the target product **3a**.

Conclusions

In conclusion, a novel approach towards biologically important dibenzo[*b*,*d*]azepines through metal- and additive-free ring expansion was developed. Remarkably, employing air as a "green" oxidant is an attractive reaction protocol for application in organic synthesis and pharmaceutical chemistry. The synthetic potential and practicality were proved by good functional group tolerance, successful scale-up experiments, and the possible expansion toward the synthesis of isoindoline derivatives. Further efforts are in progress to utilize the reaction and study the potential pharmaceutically active compounds in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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