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Synthesis of 1,4-Benzothiazines via KI/DMSO/O_2-Mediated Three-Component Oxidative Cyclization/Coupling

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Abstract. A three-component transition-metal-free aerobic method for the generation of 1,4-benzothiazines is reported herein. The KI/DMSO/O_2 system was found to be effective for the oxidative cyclization/coupling of 2-aminobenzenethiols, anilines, and methylketones. Hence, various structurally important imino 1,4-benzothiazines were assembled with broad functional group tolerance. Mechanistic studies revealed an initial oxidation of ketone α C-H bonds by the KI/DMSO/O_2 oxidative system.

Keywords: N-heterocycles; aerobic oxidation; 1,4-benzothiazines; cyclization; multi-component.

Multi-component synthesis, or combinational chemistry, is a powerful strategy for the rapid construction of complex compounds, because it is atom- and step-economical, and entails facile one-pot execution. Hence, a myriad of recent methodologies feature multi-component reactions, with extensive applications in the synthesis of valuable molecules.[1]

Heterocycles are ubiquitous in naturally occurring products, pharmaceuticals, functional materials, etc.; among them, N,S-heterocycles, such as thiazoles and thiazines, are structurally privileged compounds because they exhibit a wide range of biological activities in vivo and in vitro, such as antibacterial, antidiabetic, anti-arrhythmic, and antitumor.[2] Consequently, numerous synthetic methods have been developed for these compounds. Specifically, 2-aminobenzenethiols have been established as the most effective building blocks for the construction of benzo N,S-heterocycles,[3] although there are recent examples that access the target compounds through direct C-H sulfenylation with elemental sulfur.[4] In this regard, a number of viable systems for the heteroannulation of 2-aminobenzenethiols with carbonyls have been developed. For example, the cyclo-condensation of 2-aminobenzenethiols with carboxylic acids or aldehydes under thermal or oxidative conditions, respectively, provides an efficient entry to benzothiazoles (Scheme 1, a). Hence, ketones may be suitable coupling partners in this approach. In 2012, Wu et al. developed an I_2-promoted domino protocol for the construction of 2-acylbenzothiazoles, where simple and readily available aromatic ketones/unsaturated methyl ketones and o-aminobenzenethiols were utilized (Scheme 1, b).[5] In the same year, Deng and co-workers complementarily disclosed a facile 2-aryl benzothiazole formation from aryl ketones and 2-aminobenzenethiols under metal- and catalyst-free conditions. In this reaction, ketones underwent C-C bond cleavage, and molecular oxygen served as the terminal oxidant (Scheme 1, c).[6] In 2016, Yi and Lu reported a convergent transition-metal-free access to 1,4-benzothiazine derivatives from o-aminobenzenethiols, where the product type was dependent on the nature of the ketone, which included α,β-unsaturated, cyclic, linear, and fluoroalkyl ketones (Scheme 1, d).[7] Despite these advances, multi-component formation of N,S-heterocycles from 2-aminobenzenethiols is rarely reported and remains underdeveloped; such a methodology could facilitate the attainment of structural diversity and complexity in target products. [3g,3i] Herein, we report the facile three-component assembly of 1,4-benzothiazines from 2-aminobenzenethiols, acetophenones, and anilines under iodide-catalyzed aerobic conditions (Scheme 1, e).

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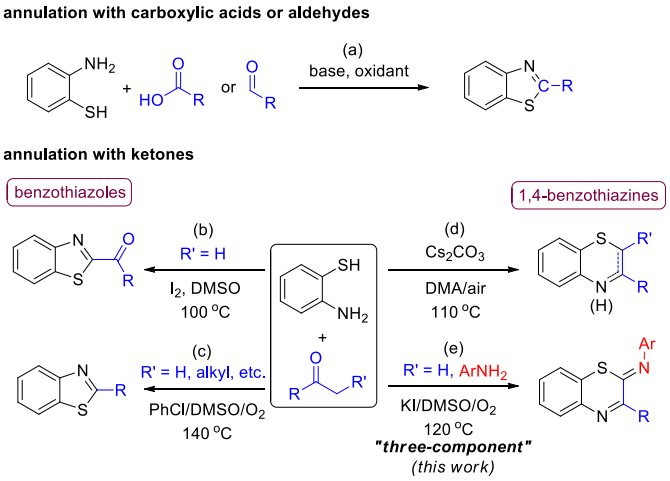
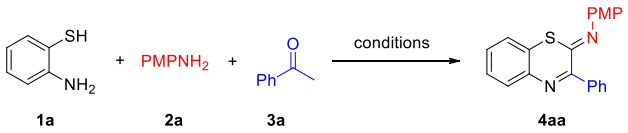


Scheme 1. Heteroannulations of 2-aminobenzenethiols with carbonyls.

Initially, 2-aminobenzenethiol **1a**, 4-methoxyaniline ($PMPNH_2$, **2a**), and acetophenone **3a** were chosen as the model substrates for the optimization of reaction conditions (Table 1). When the mixture was heated with CuI as the catalyst, under an oxygen atmosphere at 120 °C in DMSO, imino-1,4-benzothiazine **4aa** was generated in 20% GC yield (entry 1). Further studies revealed that the copper catalyst was not required and the use of KI as the catalyst furnished a comparable result (entry 2). Given that DMSO could serve as a co-oxidant in aerobic oxidation,[4e] we screened a series of solvents, where DMSO was used as an additive (4.0 equiv, entries 3-7). The results indicated that both toluene and chlorobenzene (PhCl) enhanced the formation of **4aa**, with yields of 54% and 65%, respectively, while 1,4-dioxane and 1,2-dichloroethane (DCE) quenched the reaction. Next, the use of various iodine reagents, including NaI, NH_4I, I_2, and NIS was investigated. They were all capable of furnishing the imino-1,4-benzothiazine product, albeit in slightly lower yields (entries 8-11). With the use of 3.0 equiv of DMSO, the yield of **4aa** declined slightly (entry 12). Moreover, in the absence of DMSO, the reaction afforded the target product in 47% yield (entry 13). The reaction was performed at a range of temperatures, and it was established that 120 °C was the optimal temperature (entries 14 and 15). It was observed that an oxygen atmosphere was essential to this reaction. While the reaction yield dramatically decreased in air (entry 16), only trace amounts of product were detected under an argon atmosphere (entry 17). Finally, in the absence of KI the reaction afforded only 12% product yield. Notably, in the process of optimization, 2-phenylbenzothiazole, generated by the oxidative annulations of **1a** and **3a**,[6] was frequently detected as the major side product.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4aa

Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	CuI	-	DMSO	20
2	KI	-	DMSO	21
3	KI	DMSO	DMF	18
4	KI	DMSO	toluene	54
5	KI	DMSO	1,4-dioxane	trace
6	KI	DMSO	PhCl	65 (64)
7	KI	DMSO	DCE	trace
8	NaI	DMSO	PhCl	60
9	NH_4I	DMSO	PhCl	40
10	I_2	DMSO	PhCl	32
11	NIS	DMSO	PhCl	35
12[c]	KI	DMSO	PhCl	62
13[d]	KI	-	PhCl	47
14[e]	KI	DMSO	PhCl	31
15[f]	KI	DMSO	PhCl	65
16[g]	KI	DMSO	PhCl	10
17[h]	KI	DMSO	PhCl	trace
18	-	DMSO	PhCl	12

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (PMP = 4-$MeOC_6H_4$, 0.3 mmol, 1.5 equiv), **3a** (0.3 mmol, 1.5 equiv), catalyst (0.04 mmol, 20 mol%), additive (0.8 mmol, 4 equiv), solvent (1 mL, 0.2 M), 120 °C, 16 h, under O_2 (sealed tube).
[b] GC yield with dodecane as the internal standard and isolated yield was given in parentheses.
[c] DMSO (3 equiv).
[d] Without DMSO.
[e] 110 °C.
[f] 130 °C.
[g] Under Air.
[h] Under Ar.

With the optimized reaction conditions in hand, we next probed the substrate scope of the iodide-based aerobic catalysis. With respect to acetophenones (Scheme 2), a wide range of functionalities substituted on the benzene ring was compatible with the present aerobic catalysis, including alkyl, fluoro, chloro, bromo, methoxy, nitro, and nitrile. Hence, a number of novel imino 1,4-benzothiazines were readily accessed in yields ranging from moderate to good (**4aa-4al**, 37-78%). 4-Chloroacetophenone exhibited the highest reactivity, to afford the corresponding benzothiazine (**4ad**) in 78% yield. Both electron-donating (OMe) and electron-withdrawing groups (CN, NO_2) diminished reaction

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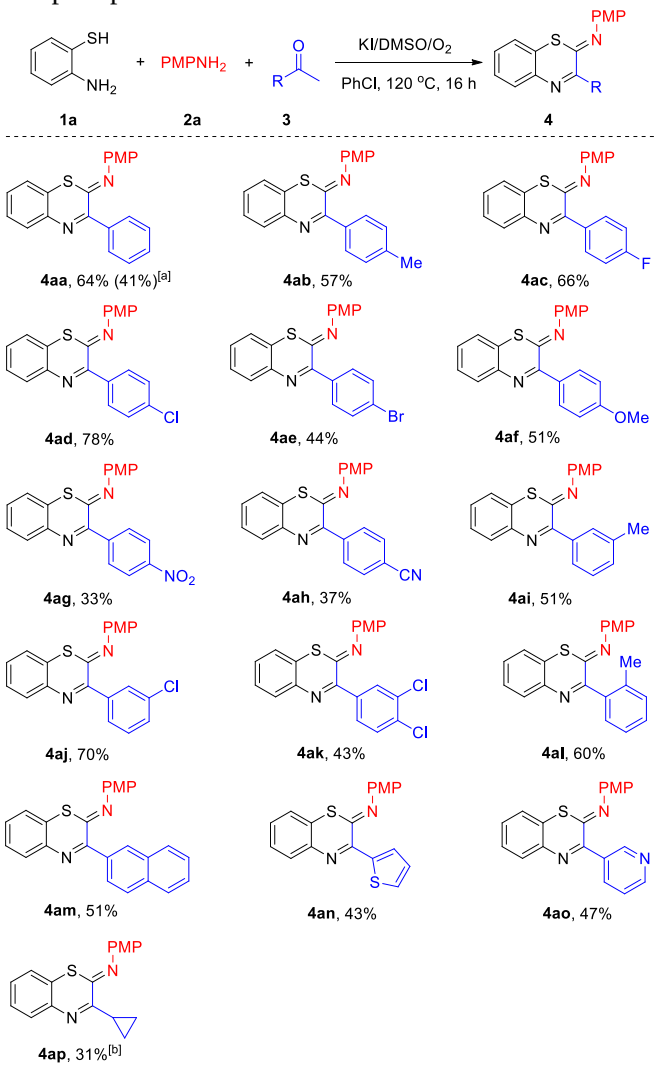
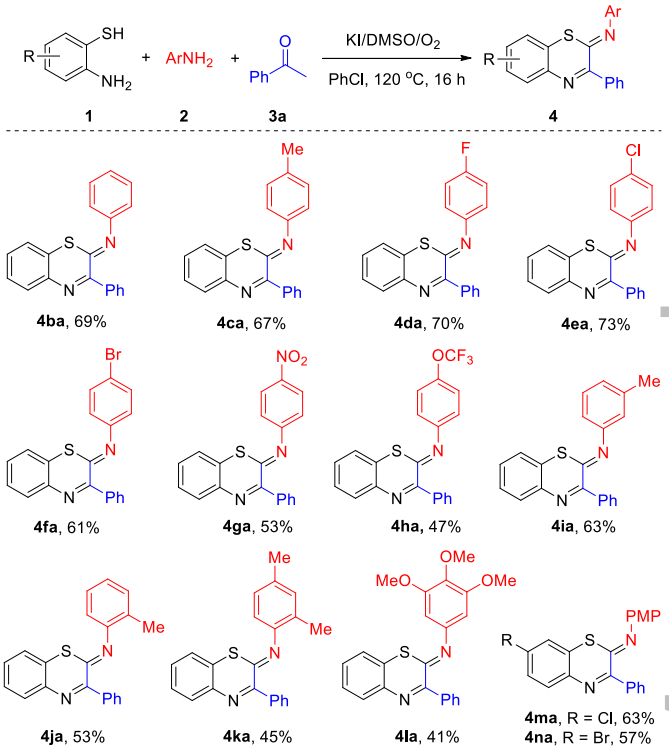
efficiency. The effect of steric hindrance was somewhat unclear (**4ab**, **4ai** versus **4al**). 1-(Naphthalen-2-yl)ethanone proved to be a suitable reactant, affording **4am** in a moderate yield. Among others, heteroaryl ketones bearing thiophenyl (**4an**) and pyridinyl (**4ao**) moieties reacted adequately in this transition-metal-free system. Aliphatic ketones exhibited lower reactivity, as exemplified by 1-cyclopropylethanone (31% yield, **4ap**). The model reaction was found to be scalable to 1.0 mmol, furnishing **4aa** in 41% yield. However, the gram-scale reaction exhibited very low reactivity to afford complex product masses in the TLC.



Scheme 2. Substrate scope with respect to ketones. [a] Yield on a 1.0 mmol scale. [b] 5 equiv of ketone were used.

Regarding the amine component, experimental results indicated that only anilines could be employed in the three-component reaction. Aliphatic amines, benzylamines, and even heteroarylamines, such as 2-aminopyridine, 4-aminopyridine, 8-aminoquinoline, and 2-aminobenzothiazole were not suitable, generally giving rise to complex product masses in the GC-MS. However, a number of typical anilines bearing functional groups including Me, halo (F, Cl, Br, **4da-4fa**), NO_2 (**4ga**), OCF_3 (**4ha**), and OMe (**4la**), were successfully transformed into the desired products (Scheme 3). The reactivity of substituted 2-aminobenzenethiol was tested by employing chloro- and bromo-substituted substrates, which afforded the corresponding products in modest yields (**4ma** and **4na**).



Scheme 3. Substrate scope with respect to anilines.

In order to elucidate the mechanism of the present oxidative three-component reaction, a number of control experiments were conducted. The interaction between aniline **2a** and ketone **3a** afforded imines **5** and **6** under the standard reaction conditions (Scheme 4, a). Expectedly, phenylglyoxal was generated by the oxidation of ketone α C-H bonds. In the absence of the aniline component, oxidative annulation products **7** and **8** were detected by GC-MS, albeit in trace amounts (Scheme 4, b), which indicated that the direct oxidative coupling of 2-aminobenzenethiol with acetophenone or phenylglyoxal was not possible in the present system. When phenylglyoxal (**9**) was used instead of acetophenone, the coupling annulation product **4aa** was obtained in 67% yield (Scheme 4, c). The above results indicate that phenylglyoxal is a likely intermediate and that it preferentially couples with anilines (**2**) over 2-aminobenzenethiol to enable further interaction. Ultimately, the three-component reaction most likely does not proceed through a radical pathway, as the addition of radical scavengers, such as TEMPO and BHT, did not quench the transformation (Scheme 4, d).

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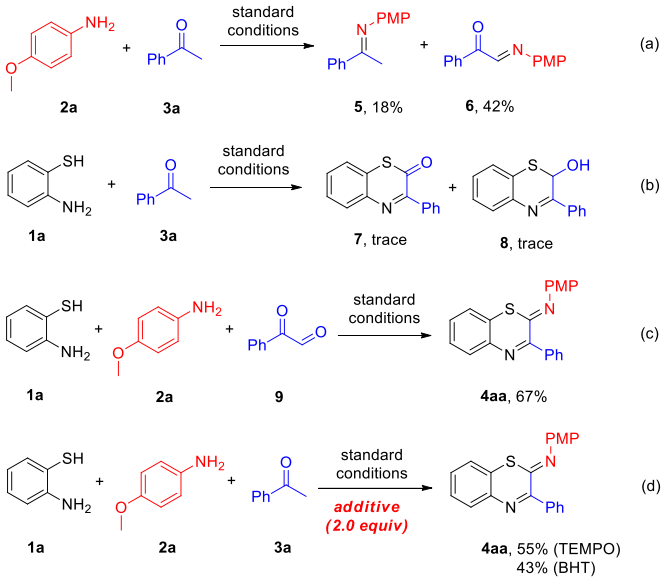
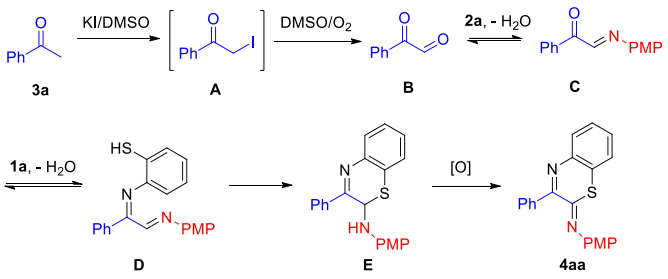


Scheme 4. Control experiments.

On the basis of experimental results and previous reports, a plausible reaction mechanism of the aerobic oxidative three-component coupling/annulation is proposed (Scheme 5). Acetophenone **3a** undergoes α-iodination to generate **A** in the presence of iodine reagent and DMSO.[8] Subsequent oxidation and oxygenation of **A**, i.e. Kornblum oxidation,[9] affords phenylglyoxal **B**, which couples with aniline **2a** to give imine **C** via aldimine condensation. Further condensation of **C** with 2-aminobenzenethiol (**1a**), followed by an intramolecular nucleophilic addition, furnishes the annulation intermediate **E**, with oxidative dehydrogenation to produce the final imino 1,4-benzothiazine **4aa**. Notably, α-iodoacetophenone **A** may directly couple with **2a**, to afford intermediate **C** following oxidation. Additionally, anilines bearing an electron-withdrawing group seemingly provide higher yields than those with electron-donating groups (Scheme 3). This result indicates that the aldimine condensation of the phenylglyoxal intermediate and aniline is not the rate-determining step. Due to the reversibility of the aldimine condensation, the regioselectivity of **B** with two anilines (**1a** and **2a**) was probably collaboratively controlled by the substrate ratio (1.5 equiv of both **2a** and **3a**) and the stability of the resultant annulation product.



Scheme 5. Plausible reaction mechanism.

In summary, we have developed an aerobic three-component oxidative annulation that employs the KI/DMSO/O_2 system and allows for a facile assembly of novel imino 1,4-benzothiazines. The reaction system enables the oxidative cyclization/coupling of readily accessible 2-aminobenzenethiols, anilines, and methylketones, to afford a new class of benzothiazine products in generally moderate to good yields. This multi-component construction of 1,4-benzothiazines complements previous oxidative cyclizations of 2-aminobenzenethiols and ketones. The protocol will hopefully inspire other novel multi-component reaction designs for heterocycle formation.

Experimental Section

General procedure for the synthesis of benzothiazole heterocycles

A 10-mL reaction vessel was charged with 2-aminothiophenol (**1a**, 0.2 mmol), 4-methoxyaniline (**2a**, 0.3 mmol), acetophenone (**3a**, 0.3 mmol), KI (0.04 mmol), DMSO (0.8 mmol), and PhCl (1.0 mL) under O_2. The mixture was then stirred at 120 °C for 16 h. After cooling to room temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic fractions were dried over magnesium sulfate and filtered. The volatiles were removed under reduced pressure and the resultant residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, R_f = 0.3) to give the desired 4-methoxy-*N*-(3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)aniline (**4aa**) as a yellow solid (44.1 mg, 64% yield). Mp: 165-167 °C.

Acknowledgements

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