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Radical Route to 1,4-Benzothiazine Derivatives from 2-Aminobenzenethiols and Ketones under Transition-Metal-Free Conditions

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Supporting Information

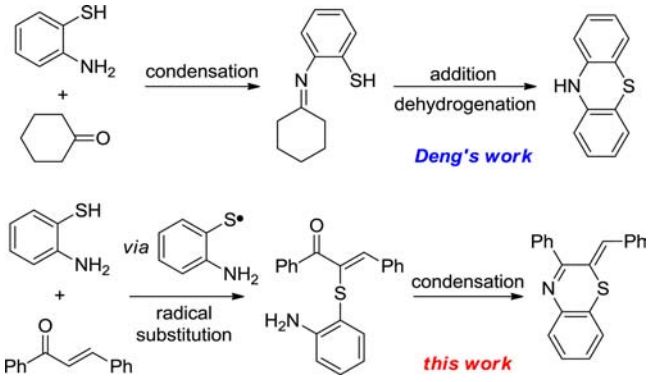
ABSTRACT: Transition-metal-free radical access to 1,4-benzothiazine derivatives from *o*-aminobenzenethiols is disclosed. This procedure is available for various ketones including α,β-unsaturated, cyclic, linear, and fluoroalkyl ketones to generate a number of 1,4-benzothiazines, which exist in numerous bioactive and natural molecules, rendering this protocol attractive to both synthetic and medicinal chemistry.

Organosulfur heterocycles are known to represent a class of important compounds because of their potential biological activity, pharmaceutical significance, and synthetic utility.[1] Among them, 1,4-benzothiazines are considered the core structures in many pharmaceutically active compounds and natural products. In addition, they show a wide range of biological activities in vivo and in vitro, such as antibacterial, antidiabetic, anti-arrhythmic, and antitumor.[2] Consequently, the development of efficient approaches for the synthesis of 1,4-benzothiazine derivatives is an appealing and valuable task to both synthetic and medicinal chemistry.

Traditionally, these compounds are synthesized by transition-metal-free condensation of *o*-aminobenzenethiols with β-diketones or organic halides.[3] Nevertheless, these strategies suffer from the need for prepreparation of the starting materials, narrow substrate scope, and poor regioselectivity. To solve these issues, various transition-metal-catalyzed cross-coupling reactions have been well-developed for the construction of 1,4-benzothiazines.[4,5] Although transition-metal-catalyzed cross-couplings have proved to be very useful tools for the selective formation of 1,4-benzothiazine derivatives, the use of toxic transition-metal catalysts goes against the low threshold residual tolerance of metals in pharmaceutical fields. Therefore, the exploration of transition-metal-free strategies that have high regioselectivity and broad substrate scope using cheap and easy-to-handle substrates is still highly desirable.

On the one hand, Deng and co-workers reported the selective formation of phenothiazine from 2-aminobenzenethiols and cyclohexanones using molecular oxygen as a hydrogen acceptor under metal-free conditions at high temperature (140 °C) (Scheme 1).[6] On the other hand, thiyl radicals as the center of some extremely efficient radical reactions for the synthesis of organosulfur compounds[7] may have unique reactivity compared with sulfide cations and anions in terms of electronic effects and substrate scope. Therefore, we reasoned that the thiyl radical as the prior reaction center would be a better option than the amino group because radical substitution is easier than condensation.[6,8] Along this line, here we disclose the first example of radical access to various 1,4-benzothiazine derivatives from 2-aminobenzenethiols and ketones under transition-metal-free conditions (Scheme 1).

Scheme 1. Transtion-Metal-Free Strategies for the Generation of 1,4-Benzothiazines from 2-Aminobenzenethiols and Ketones



We started the investigation by selecting the reaction of 2-aminobenzenethiol (**1a**) with chalcone (**2a**) as the model reaction (Table 1). To our delight, the reaction provided a 61% yield of the desired product **3a** using Cs_2CO_3 as the base (entry 1). After screening of different amounts of the base, 0.5 equiv of Cs_2CO_3 emerged as the best option (entries 1−4). In addition, the types of solvent and base were also optimized in the reaction, and the combination of methanol and Cs_2CO_3 was the best choice (entry 8). The reaction was inhibited at lower temperature (entry 15). No reaction took place in the absence of base (entry 16). A poor yield was provided under an atmosphere of N_2, indicating that air is beneficial to the process

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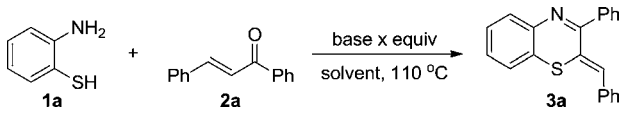
Table 1. Optimization of the Reaction Conditions[a]



entry	base	x	solvent	yield (%)[b]
1	Cs_2CO_3	2	DMSO	61
2	Cs_2CO_3	1	DMSO	65, 55[c]
3	Cs_2CO_3	0.5	DMSO	60
4	Cs_2CO_3	0.3	DMSO	41
5	Cs_2CO_3	0.5	H_2O	nr
6	Cs_2CO_3	0.5	1,4-dioxane	40
7	Cs_2CO_3	0.5	DMF	42
8	Cs_2CO_3	0.5	MeOH	91, 86[d]
9	K_2CO_3	0.5	MeOH	80
10	DBU	0.5	MeOH	40
11	*t*-BuOK	0.5	MeOH	56
12	NaOH	0.5	MeOH	62
13	Cs_2CO_3	0.5	EtOH	32
14	Cs_2CO_3	0.5	DMAc	37
15	Cs_2CO_3	0.5	MeOH	59[e]
16	Cs_2CO_3	0	MeOH	32
17	Cs_2CO_3	0.5	MeOH	18[f]
18	Cs_2CO_3	0.5	MeOH	78[d,g]

[a]Reaction conditions: **2a** (0.250 mmol), **1a** (0.375 mmol), base (*x* equiv), solvent (1.0 mL), 110 °C, 10 h, air. [b]GC yields. [c]0.1 equiv of CuI was added. [d]Isolated yield. [e]80 °C. [f]Under N_2 atmosphere. [g]Reaction conditions: **2a** (5.0 mmol), **1a** (7.5 mmol), Cs_2CO_3 (0.5 equiv), MeOH (5.0 mL), 110 °C, 24 h, air.

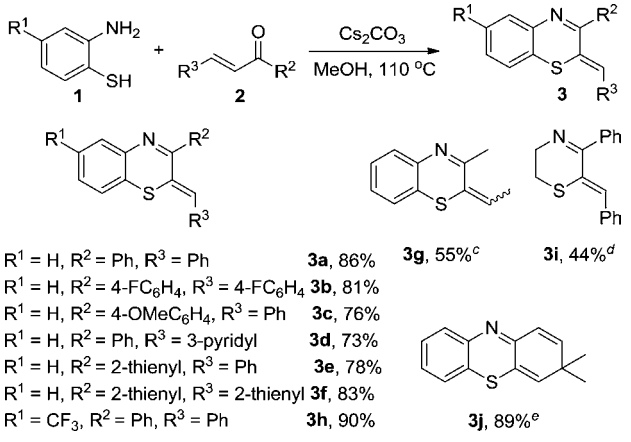
(entry 17). Meanwhile, we scaled up the model reaction to 5 mmol to show the possibility for large-scale operation (entry 18), and a satisfactory yield (78%) was obtained by prolonging the reaction time to 24 h.

With the optimized conditions in hand, a series *α,β*-unsaturated ketones were applied in the reaction to established the scope and generality of this protocol (Scheme 2). Chalcones containing electron-donating or electron-withdrawing groups could react with **1a** to give the corresponding 1,4-benzothiazines in moderate to excellent yields (**3a–c**). Heterocyclic-substituted chalcones were also successfully applied in the reaction with satisfactory results (**3d–f**). A cyclic *α,β*-unsaturated ketone provided the corresponding product **3j**, presumably as a result of base-induced dehydrogenation.[10] The configuration of the final product remained unsure when an alkyl *α,β*-unsaturated ketone was used (**3g**). In addition, the reaction was sluggish when 2-aminoethane-1-thiol was used (**3i**).

It should be noted that phenothiazines that were widely employed in the design of various pharmaceuticals[9] could also be generated in this system by switching the substrates from *α,β*-unsaturated ketones to cyclohexanones. DMSO proved to be the best solvent, and base was not essential for this reaction. Reactions of cyclohexanones occurred in moderate to good yields (**4a–e**; Scheme 3). 2-Aminoethane-1-thiol was applied to generate the 1,4-benzothiazine ring in lower yield (**4g**). Moreover, cycloheptanone and cyclohexanedione could also undergo this reaction with a change in the base and solvent (**4f**, **4h**). To our delight, linear ketones could also react with **1** to form 1,4-benzothiazine derivatives **5a–c** in moderate to good yields (Scheme 4). However, aliphatic ketones (e.g., pentan-3-one and butan-2-one) failed to give the corresponding products in the protocol.

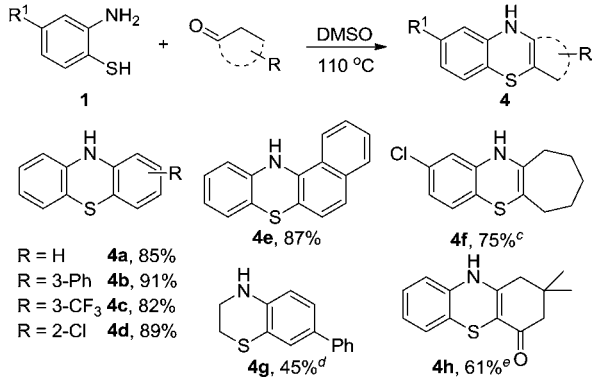
The incorporation of fluoroalkyl substituents into heterocyclic compounds has attracted specific interest because of their ability to enhance the metabolic stability and membrane permeability of the parent molecules.[11] In addition, fluoroalkyl

Scheme 2. Reaction of *o*-Aminobenzenethiols with *α,β*-Unsaturated Ketones[a,b]



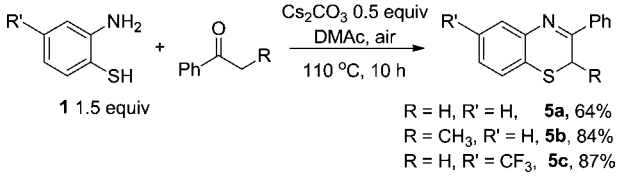
[a]Reaction conditions: **2** (0.250 mmol), **1** (0.375 mmol), Cs_2CO_3 (0.125 mmol), MeOH (1.0 mL), 110 °C, 10 h, air. [b]Isolated yields are shown. [c]The configuration of **3g** was uncertain. [d]2-Aminoethane-1-thiol was used. [e]4,4-Dimethylcyclohex-2-en-1-one was used.

Scheme 3. Reaction of *o*-Aminobenzenethiols with Cyclic Ketones[a,b]



[a]Reaction conditions: cyclic ketone (0.250 mmol), **1** (0.375 mmol), DMSO (1.0 mL), 110 °C, 24 h, air. [b]Isolated yields are shown. [c]Reaction conditions: cycloheptanone (0.250 mmol), **1a** (0.375 mmol), Cs_2CO_3 (0.125 mmol), MeOH (1.0 mL), 110 °C, 10 h, air. [d]2-Aminoethane-1-thiol was used. [e]Reaction conditions: 5,5-dimethylcyclohexane-1,3-dione (0.250 mmol), **1a** (0.375 mmol), DBU (0.500 mmol), DMSO (1.0 mL), 110 °C, 10 h, air.

Scheme 4. Reaction of *o*-Aminobenzenethiols with Linear Ketones



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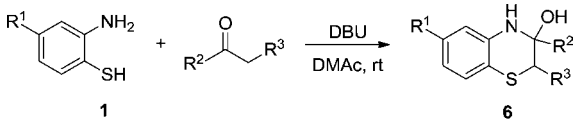
as a strong electron-withdrawing group significantly increases the electrophilicity of the carbonyl group in ketones. Thus, we treated fluoroalkyl ketones with *o*-aminobenzenethiols under basic conditions, and the fluoroalkyl 1,4-benzothiazines were obtained fortunately. In all cases, only tetrahedral adducts were produced in moderate to good yields (**6a**–**e**; Scheme 5).[12]

Scheme 5. Reaction of *o*-Aminobenzenethiols with Fluoroalkyl Ketones[a,b]



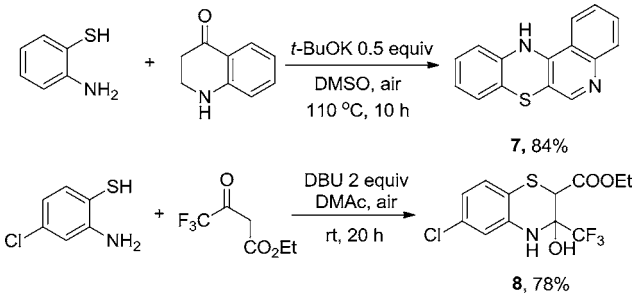
1 **6**

R^1 = Cl, R^2 = CF_2H, R^3 = H **6a**, 44%
R^1 = Cl, R^2 = CF_3, R^3 = H **6b**, 85%
R^1 = Cl, R^2 = C_4F_9, R^3 = H **6c**, 71%
R^1 = Cl, R^2 = C_2F_5, R^3 = COOEt **6d**, 63%
R^1 = CF_3, R^2 = CF_3, R^3 = H **6e**, 91%

[a]Reaction conditions: fluoroalkyl ketone (0.375 mmol), **1** (0.250 mmol), DBU (0.500 mmol), DMAc (1.0 mL), rt, 24 h, air. [b]Isolated yields are shown.

To further demonstrate the potential of the chemistry, azaphenothiazine **7**, whose derivatives have antiproliferative activity toward cancer cells,[13] was synthesized under identical conditions (Scheme 6). Likewise, compound **8** derived from 2-amino-4-chlorobenzenethiol and ethyl 4,4,4-trifluoro-3-oxobutanoate (Scheme 6) could be transformed into the corresponding 4*H*-1,4-benzothiazine and sulfone, which are possible antibacterial and antifungal agents, through dehydration and oxidation routes, respectively.[14]

Scheme 6. Synthesis of Potential Drug Intermediates 7 and 8



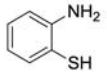
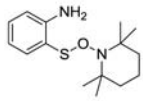
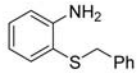
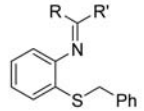
7, 84%

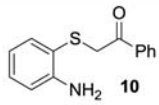
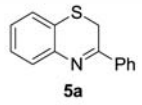
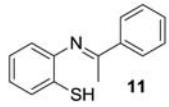
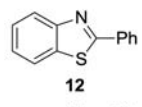
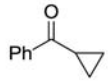
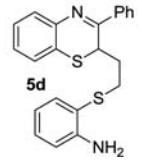
8, 78%

Further control experiments were performed to probe the mechanism (Table 2). All four reactions were inhibited in the presence of TEMPO, and the radical trapping products were observed in these reactions by GC–MS (entries 1–4). These results suggest that the transformation may include a radical process. Only the undesired ring-opening product **5d** could be detected in the case of cyclopropyl(phenyl)methanone as a radical clock experiment, further confirming the existence of a radical intermediate (entry 12).[7g]

In order to find out the prior reaction center during the cyclization reaction, **9** was reacted with five ketones under optimized conditions (entries 5–9). Only acetophenone led to a 15% yield of the condensation product. Compound **10** may be the intermediate during the reaction since it can be transformed into the desired product **5a** even at lower temperature (entry 10). Compound **11** failed to yield **5a**, and **12** was obtained as a byproduct (entry 11). On the basis of these results, it can be concluded that (1) the condensations between ketones and amines are difficult in these systems; (2) the initial step may be addition of the thiyl radical to the ketone; (3) the condensation products cannot afford 1,4-benzothiazines under identical conditions;[15] (4) the intramolecular condensation is easier than the intermolecular condensation (entry 8 vs 10).[8,16]

Table 2. Control Experiments

entry	thiol or amine	condition[a]	trapping or condensation product	yield (%)[b]
1	 **1a**	A		14[c]
2		B		0[c]
3		C		0[c]
4		D		0[c]
5	 **9**	A		0
6		B		trace
7		C		trace
8		C[d]		15
9		D		0

entry	substrate	condition	product	yield (%)[e]
10	 **10**	Cs_2CO_3 0.5 equiv DMAc air 10 h	 **5a**	95[f]
11	 **11**		 **12**	36[g]
12			 **5d**	70[h]

[a]Condition A: chalcone (0.250 mmol), **1a** or **9** (0.375 mmol), Cs_2CO_3 (0.125 mmol), MeOH (1.0 mL), 110 °C, 10 h, air. Condition B: cyclohexene (0.250 mmol), **1a** or **9** (0.375 mmol), DMSO (1.0 mL), 110 °C, 24 h, air. Condition C: propiophenone (0.250 mmol), **1a** or **9** (0.375 mmol), Cs_2CO_3 (0.125 mmol), DMAc (1.0 mL), 110 °C, 10 h, air. Condition D: 1,1,1-trifluoropropan-2-one (0.375 mmol), **1a** or **9** (0.250 mmol), DBU (0.500 mmol), DMAc (1.0 mL), rt, 24 h, air. [b]GC yields of 1,4-benzothiazines. [c]3.0 equiv TEMPO was used. [d]Acetophenone was used instead of propiophenone. [e]Isolated yields. [f]50 °C. [g]110 °C. [h]3 equiv of **1a** was used.

Although the detailed mechanism of this reaction remains to be elucidated, a tentative pathway for the cyclization of ketones and 2-aminobenzenethiols is proposed in Scheme 7. Initially, thiyl radical **13** generated in situ from the 2-aminobenzenethiol upon heating under an air atmosphere adds to the enol formed by isomerization of the ketone to afford carbon radical intermediate **14**, after which a single electron transfer process produces **15**. Intermediate **15** can be transformed into the final product by an intramolecular condensation route. If the condensation product **16** is generated in some cases, it can be further condensed to provide the 2-substituted benzothiazole byproduct.[15] The base plays a dual role in the reaction: (1) enhancing the nucleophilicity of enol and (2) promoting the intramolecular condensation process.

In summary, we have developed an efficient approach for the generation of various 1,4-benzothiazine rings from 2-aminobenzenethiols and ketones under transition-metal-free con-

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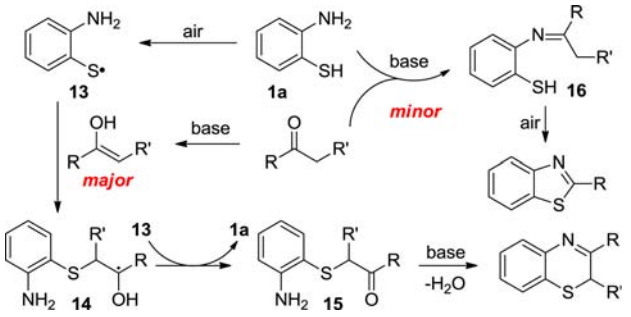
Scheme 7. Tentative Pathway for the Reaction of 2-Aminobenzenethiols with Ketones



ditions. The significance of the present chemistry is threefold: (1) This research reveals the first example of the formation of 1,4-benzothiazine derivatives via a radical pathway. (2) The strategy is free of transition metals and the starting materials are conveniently available, making this approach more suitable for pharmaceutical synthesis. (3) The efficiency of this procedure has been fully demonstrated by synthesizing a number of new 1,4-benzothiazine derivatives, opening a new window of opportunities that may be available for new drug discovery from this scaffold.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03324.

Experimental details and copies of NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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