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Metal-free oxidative cascade cyclization of isocyanides with thiols: a new pathway for constructing 6-aryl(alkyl)thiophenanthridines

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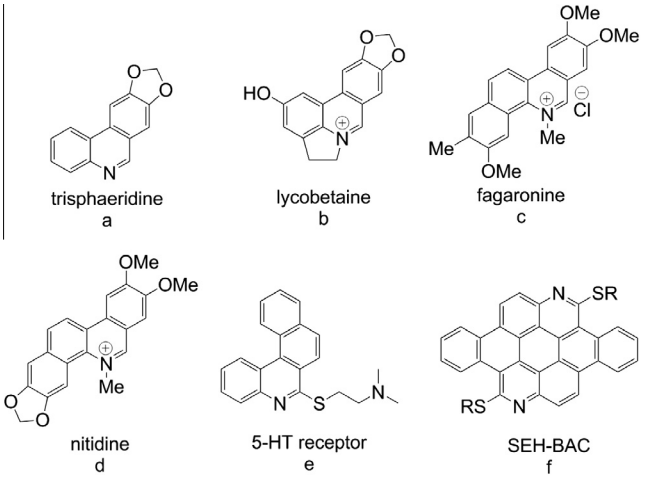
ABSTRACT

A metal-free pathway for constructing 6-aryl(alkyl)thiophenanthridines through oxidative cascade cyclization of isocyanides with thiols is developed. This pathway is characterized by S—H bond cleavage of commercially available thiols, and subsequent C—S/C—C bond formation, which is suitable for a wide scope of substrates and by which a variety of 6-aryl(alkyl)thiophenanthridines could be synthesized in good to excellent yields.

Introduction

Phenanthridine skeletons as a kind of significant nucleus exist in nature products commonly, these phenanthridine-containing compounds show antiviral, antibacterial, antitumoral, and antileukemic activity[1–7] (Scheme 1a–d). Therefore, the development of novel methods for their preparation is necessary, and in recent years, diverse methods have been developed for the synthesis of phenanthridine derivatives.[8–16] In addition to the traditional methods, phenanthridines have recently been successfully prepared by radical chemistry using cascades of radical addition to 2-isocyanobiphenyls with subsequent homolytic aromatic substitution (HAS), and several groups have successively reported their efforts to synthesize phenanthridine derivatives,[17–26] through intramolecular cyclization of active radical intermediates which were formed in-situ by coupling reactions of 2-isocyanobiphenyls with C-, P-, Si- or O-containing radicals, respectively.

6-Alkylthiophenanthridines have been successfully applied in pharmaceutical industry[27–29] and materials science[30] (Scheme 1e and f); so far, as we know the reports on constructing phenanthridine derivatives in radical pathway by C—S bond formation are limited,[31] these methods usually required not only a large number of disulfides (6 equiv) but also oxidants (6 equiv) in order to obtain satisfying yields. As mentioned above, we believed in that it is still desirable to develop a new radical pathway to directly construct phenanthridine derivatives using inexpensive, commercially available and S-containing low dose substrates. Additionally, we know that disulfides are traditionally derived from thiols,[32–37] so we spontaneously wonder if we could use thiols as sulfur source in place of disulfides to synthesize 6-alkylthiophenanthridines by the formation of C—S bond, it will be a straightforward and an atom-economic strategy. To the best of our knowledge, whether metal or metal-free catalyzed synthesis of phenanthridine through coupling of thiols with isocyanobiphenyls has been not reported so far. Herein, we disclose a metal-free radical oxidative cyclization of



Scheme 1. Examples of typical phenanthridine alkaloids, pharmaceutical molecules and material with a phenanthridine core structure.

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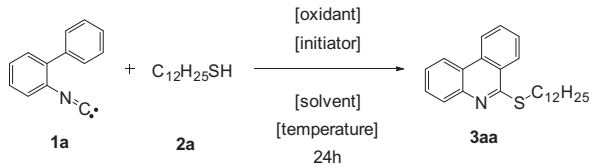
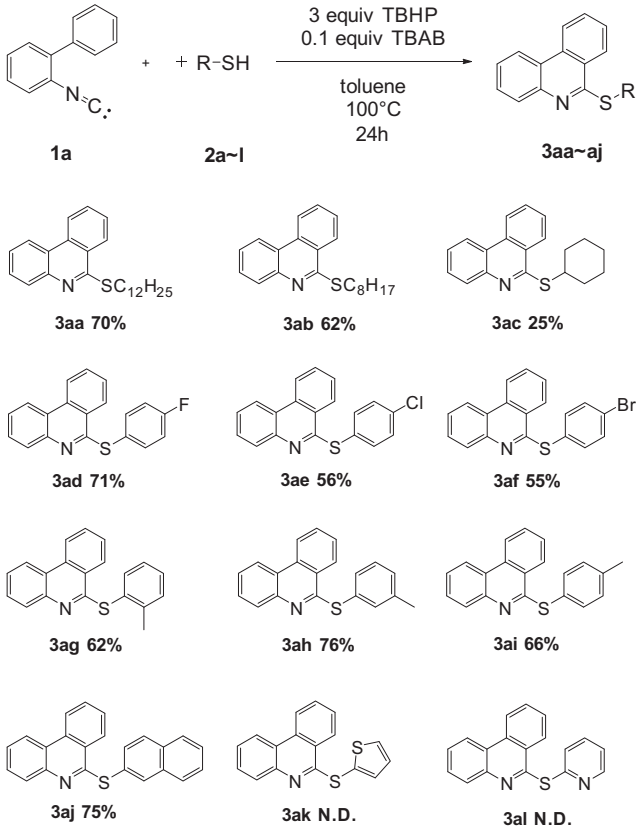
Table 1
Optimization of the reaction conditions[a]



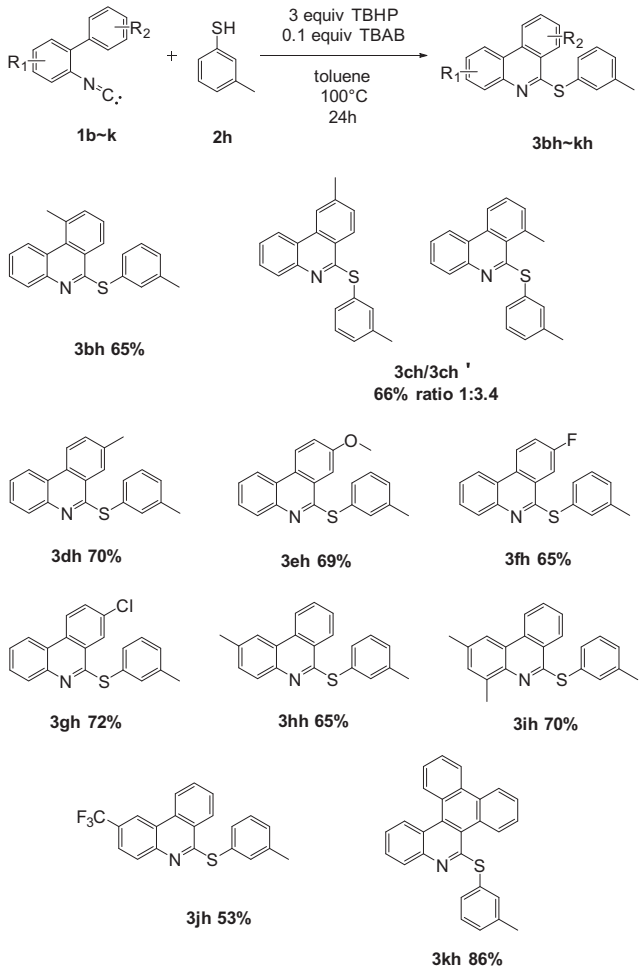
1a 2a 3aa

Entry	Oxidant	Initiator	Solvent	Yield[b] (%)
1	TBHP[c]	TBAI	Toluene	18
2	TBHP	TBAB	Toluene	70
3	TBHP	TEAB	Toluene	60
4	TBHP	CTAB	Toluene	61
5	TBHP	/	Toluene	17
6	KPS	TBAB	Toluene	35
7	DCP	TBAB	Toluene	38
8	DTBP	TBAB	Toluene	61
9	TBPB	TBAB	Toluene	52
10	TBHP	TBAB	DMSO	29
11	TBHP	TBAB	H_2O	27
12	TBHP	TBAB	1,4-Dioxane	52
13	TBHP	TBAB	Chlorobenzene	51
14	TBHP	TBAB	Toluene	47[d]
15	TBHP	TBAB	Toluene	70[e]
16	TBHP	TBAB	Toluene	52[f]

[a] Reaction conditions: All reactions were run with **1a** (2 equiv), **2a** 0.2 mmol (1 equiv), oxidant (3 equiv) and initiator (10 mol %) in toluene 2 mL at 100 °C for 24 h, protected by argon.
[b] Isolated yield of **3aa**.
[c] TBHP 70% aqueous solution.
[d] Reaction temperature: 80 °C.
[e] Reaction temperature: 120 °C.
[f] Under an air atmosphere.



Scheme 2. Scope of thiols. Reactions were run with **1a** (2 equiv), 2 0.2 mmol (1 equiv), TBHP (3 equiv) and TBAB (10 mol %) in toluene 2 mL at 100 °C 24 h, protected by argon. And yields refer to isolated yield.



Scheme 3. Scope of isonitriles. Reactions were run with **1** (2 equiv), **2h** 0.2 mmol (1 equiv), TBHP (3 equiv) and TBAB (10 mol %) in toluene 2 mL at 100 °C 24 h, protected by argon. And yields refer to isolated yield.

thiols with isocyanobiphenyls under mild conditions for constructing 6-aryl(alkyl)thiophenanthridines.

Results and discussion

To test our hypothesis, we performed the model reaction of 2-isocyanobiphenyl (**1a**, 0.4 mmol) with 1-dodecanethiol (**2a**, 0.2 mmol) using TBHP (*t*-BuOOH, 0.6 mmol) as the oxidant, TBAI (tetrabutylammonium iodide) as the original initiator, and toluene as the solvent at 100 °C under argon atmosphere (Table 1). To our delight, after 24 h, the desired product **3aa** was isolated in 18% yield and confirmed by NMR (entry 1). To improve the yield, different reaction parameters including initiators, oxidants and bases were screened. Firstly, various initiators were investigated and it was satisfying that the yield of **3aa** increased up to 70% employing TBAB (tetrabutylammonium bromide) as the initiator (entry 2); however, TEAB (tetraethylammonium bromide) or CTAB (cetyltrimethylammonium bromide) used as the initiator led to a slightly decreased yield, respectively (60%, 61%, entries 3 and 4); unfortunately, the yield extremely dropped to 17% in absence of an initiator (entry 5). Then, using TBAB as the best initiator, we selected oxidants such as KPS (potassium persulfate), DCP (dicumyl peroxide), DTBP (di-*tert*-butyl peroxide) and TBPB (*tert*-butylperbenzoate) to optimize this reaction, but these oxidants failed to improve the yield further more (entries 6–9); enlightened by relative precedent reports,[38–41] we attempted to add 1 equiv of base to this reaction system, and interestingly found that other