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Metal-free direct thiocarbamation of imidazopyridines with carbamoyl chloride and elemental sulfur†

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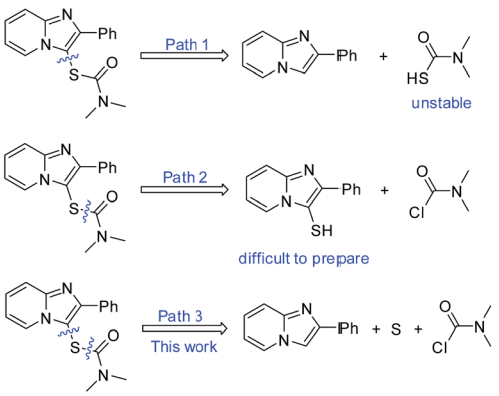
The combination of elemental sulfur and carbamoyl chloride was found to act as a carbamothioyl group surrogate for direct thiocarbamation of imidazopyridines in the absence of a metal catalyst.

Thiocarbamates are a class of important biologically active molecules, being widely used as herbicides (*e.g.* thiobencarb, orbencarb, molinate), fungicides, pesticides, and antiviral agents.[1] Traditional methods for the synthesis of thiocarbamates mainly involve the reaction of thiols with carbamoyl chloride, or the nucleophilic addition of isocyanates with thiols.[2] Iodine-catalyzed reaction of isocyanides with thiosulfonates is also an effective pathway to thiocarbamates.[3] Transition metal-catalyzed or metal-free carbonylation of carbon monoxide with thiols and amines is an alternative to access thiocarbamates.[4,5] Although odorous thiols are effective for the synthesis of thiocarbamates, their toxicity and instability are still a long-standing problem. The development of benign agents and straightforward pathways for the synthesis of thiocarbamates is greatly desired. Direct thiocarbamation of imidazopyridines is of great interest because imidazopyridines are important drug skeletons possessing a broad range of biological activities.[6,7] Great efforts have been devoted to the thiolation of imidazopyridines using thiols or disulphides.[8,9] In 2016, our group also developed a I_2/FeF_3 catalyzed direct dithiocarbamation of imidazoheterocycles with tetramethylthiuram disulphide.[9] However, no example for the direct monothiocarbamation of heterocycles is reported. The C–H thiocarbamation reactions remains to be explored. The facing challenge is that thiocarbamating agents are not available for such transformation. The development of carbamothioyl group surrogates for the direct thiocarbamation of imidazopyridines is a solution to this problem. As shown in Scheme 1, three possible pathways for retrosynthesis of imidazopyridines-thiocarbamates are given. In path 1, carbamothioic S-acid is extremely unstable and commercially unavailable. In path 2, 2-phenylimidazo[1,2-*a*]pyridine-3-thiol is not easily prepared. We envisaged that whether the combination of elemental sulfur and carbamoyl chloride could play as carbamothioyl groups surrogate for the thiocarbamation of imidazopyridines (path 3). This one-pot three-component thiocarbamation reaction is greatly desired. Because these substrates are commercially available and readily prepared, particularly the elemental sulfur is an eco-friendly agent for the synthesis of sulfur-containing compounds.[10–12] Very recently, our group also developed a metal-free oxidative dual C–H thiolation of imidazopyridines with inert alkanes or ethers using elemental sulfur.[12a] This research progress encourages us to develop a metal-free direct thiocarbamation of imidazopyridines using the combination of elemental sulfur and carbamoyl chloride as carbamothioyl groups surrogate (Scheme 1, path 3).

Our studies began with the three-component thiolation of imidazopyridine **1a** with elemental sulfur and dimethylcarbamoyl chloride. The reaction proceeded with two equivalents of DABCO in DCE at 120 °C for 24 hours, affording product **3** in 26% yield (Table 1, entry 1). Other solvents, such as DMSO,



Scheme 1 Retrosynthesis of imidazopyridines-thiocarbamates.

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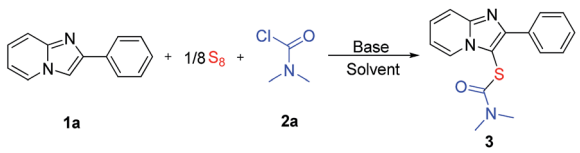
Table 1 Screening of optimal conditions[a]



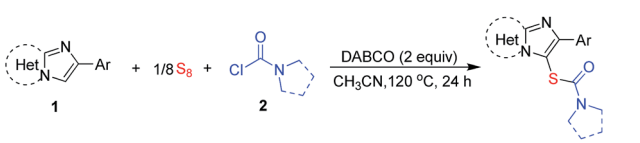
Entry	Solvent	Base (eq.)	Temp (°C)	Yield (%)
1	DCE	DABCO (2)	120	26
2	DMSO	DABCO (2)	120	0
3	DMF	DABCO (2)	120	9
4	Toluene	DABCO (2)	120	0
5	Dioxane	DABCO (2)	120	3
6	CH_3CN	DABCO (2)	120	78
7	CH_3CN	DABCO (2)	100	65
8	CH_3CN	DABCO (2)	80	33
9	CH_3CN	Et_3N (2)	120	55
10	CH_3CN	Bu_3N (2)	120	61
11	CH_3CN	Pyridine (2)	120	65
12	CH_3CN	DMAP (2)	120	68
13	CH_3CN	KOH (2)	120	32
14	CH_3CN	K_2CO_3 (2)	120	27
15	CH_3CN	DABCO (1)	120	72
16	CH_3CN	DABCO (0.5)	120	68
17	CH_3CN	—	120	48

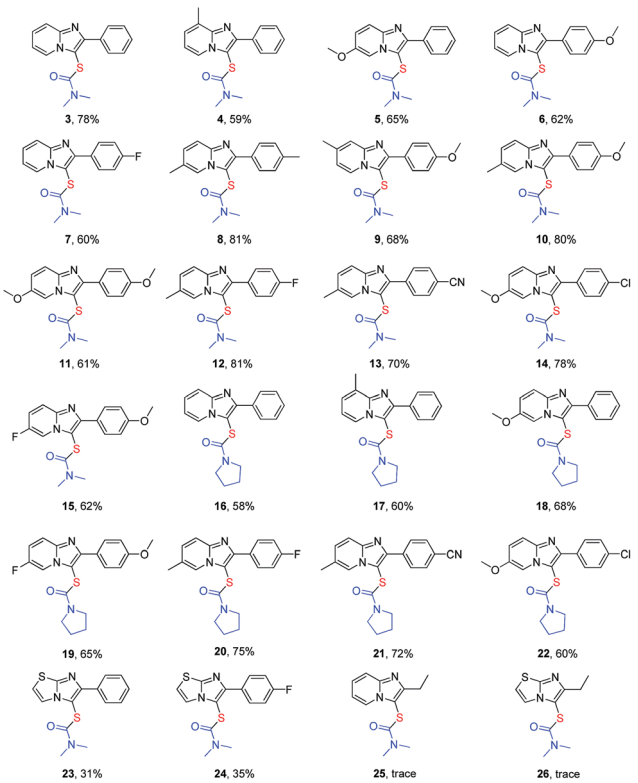
[a] Reaction conditions: **1a** (0.2 mmol), S_8 (0.4 mmol, 2 equiv.), **2a** (0.4 mmol, 2 equiv.), base, solvent (2 mL) at 120 °C for 24 h. DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine.

DMF, toluene, dioxane, and CH_3CN, were also investigated (Table 1, entries 2–6). Solvent effect has great influence on the yield. No product was found when the reaction was conducted in DMSO or toluene (Table 1, entries 2 and 4). The reaction in DMF only gave product **3** in 9% yield (Table 1, entry 3). In the reaction using DMSO as the solvent, 1,1,3,3-tetramethylurea was observed by GC-MS analysis. It suggests that carbamoyl chloride is unstable in DMSO at 120 °C, which may be the reason for no product formation. In other poor reactions, most of the starting materials **1a** was recovered (Table 1, entries 3–5). These results demonstrate that high polar (*e.g.* DMSO and DMF) and low polar solvents (*e.g.* toluene) are not suitable for this transformation under the same conditions. Interestingly, CH_3CN was found to be effective for this reaction, giving the desired product **3** in 78% yield (Table 1, entry 6). The suitable polarity of CH_3CN may facilitate the bonds cleavage of S_8 and stabilize reaction intermediates to promote the thiocarbamation. The reaction depends on not only the solvent effect but also the reaction temperature. Decreasing the temperature resulted in a sharp decrease in yield, *e.g.* 65% yield at 100 °C, 33% yield at 80 °C (Table 1, entries 7 and 8). Other bases including Et_3N, Bu_3N, pyridine, DMAP, KOH, and K_2CO_3 were examined, but these bases were less effective than DABCO (Table 1, entries 9–14). Reducing the loading of DABCO led to a decrease in the yield (entries 15 and 16). When DABCO was reduced to 1 or 0.5 equivalent, the yield was decreased to 72% and 68%, respectively. In the absence of DABCO, the reaction still occurred in CH_3CN at 120 °C, affording the product **3** in 48% yield (Table 1, entry 17). DABCO used here may play as an acid-binding agent to facilitate the transformation, because the *in situ* formed hydrogen chloride may suppress the reaction.

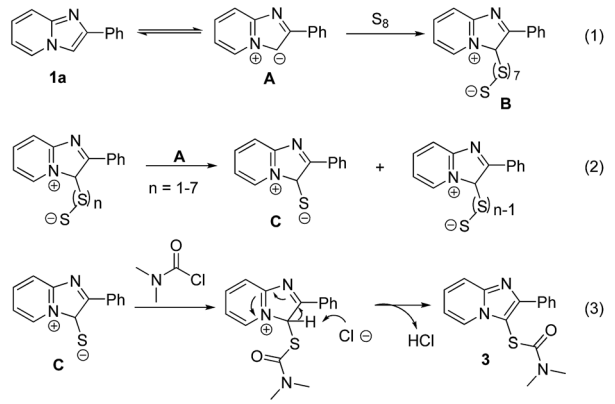
With this thiocarbamation procedure in hand, the imidazopyridine scope was investigated (Table 2). A variety of imidazopyridines were subjected to the reaction with elemental sulfur and carbamoyl chloride (products **3–15**). Substrates bearing a methyl, methoxy, or fluoro group were well tolerated affording the corresponding products in moderate to good yields (products **4–7**). Substrates bearing two substituents also have good reactivity under reaction conditions (products **8–15**). For example, the substrate bearing a methyl and a cyano groups gave product **13** in 70% yield, and the substrate bearing a methoxy and a chloro groups afforded product **14** in 78% yield. To our delight, pyrrolidine-1-carbonyl chloride also underwent the thiocarbamation smoothly to afford their corresponding products **16–22** in moderate yields. Functional groups, including methoxy, fluoro, chloro, and cyano groups, were well tolerated in the reaction. However, imidazothiazoles

Table 2 Direct thiocarbamation of imidazopyridines[a]





[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2 equiv.), S_8 (2 equiv.), DBACO (2 equiv.), in CH_3CN (2 mL) at 120 °C for 24 h.



Scheme 2 A possible reaction mechanism.

are less effective than imidazopyridines, affording poor yields under reaction conditions (products **23** and **24**). The reaction may depend on the electronic effect of the imidazole ring. The electron-rich substrate facilitates the reaction. Both 2-ethylimidazo[1,2-*a*]pyridine and 2-ethylimidazo[2,1-*b*]thiazole are not suitable substrates for such transformation. These results demonstrate that the conjugated effect between the imidazole ring and the benzene ring may be a key factor to the reactivity. The electronic effect of substituent on the benzene ring has influence on the yield to some extent. Electron-donating groups gave higher yields than electron-withdrawing ones (*e.g.* product **10** *vs.* product **13**, product **18** *vs.* product **22**, product **20** *vs.* product **21**).

In order to elucidate the reaction mechanism, the reaction of imidazopyridine **1a** with S_8 was conducted in the absence of carbamoyl chloride. LC-MS analysis showed that a small amount of di-imidazopyridinyl sulfide and di-imidazopyridinyl disulfide are formed under reaction conditions. Based on present results and previous reports concerning the thiolation using elemental sulfur,[12] a possible mechanism has been proposed as shown in Scheme 2. Under heating conditions, imidazopyridine **1a** may has a resonance structure **A**, which undergoes a nucleophilic reaction with S_8 to produce intermediate **B** (Scheme 2, eqn (1)). The polysulfide intermediate **B** reacts with **A** to provide intermediate **C** (Scheme 2, eqn (2)). Finally, the newly formed intermediate **C** undergoes a thioesterification with carbamoyl chloride to provide imidazopyridines-thiocarbamates (Scheme 2, eqn (3)).

Conclusion

In summary, the combination of elemental sulfur and carbamoyl chloride has been developed as the carbamothioyl groups surrogate for direct thiocarbamation of imidazopyridines. This metal-free three-component thiocarbamation reaction proceeds well in the presence of DABCO, giving their corresponding products in moderate to good yields. It is noteworthy that elemental sulfur is an inexpensive, nontoxic, odorless, stable and easy to handle powder; elemental sulfur also allows for an efficient synthesis of sulfur-containing compounds in terms of atom economy. These newly formed imidazopyridines-thiocarbamates may have significantly biological activity, which will be of great interest in medicinal chemistry. The direct thiocarbamation of heterocycles with elemental sulfur and formamide is underway in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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