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Tandem Approach for the Synthesis of 3-Sulfenylimidazo[1,5-*a*]pyridines from Dithioesters

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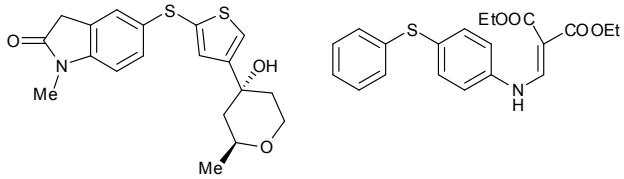
Iodine-mediated synthesis of 3-sulfenylimidazo[1,5-*a*]pyridines via C–H functionalization has been achieved using dithioesters, 2-methylaminopyridines and sulfonyl hydrazides. A library of 3-sulfanylimidazopyridines and imidazopyridines with broad functionalities are synthesized under metal-free reaction conditions.

The development of C–S bond formation has gained much attention in the organic synthesis due to the occurrence of the C-S bond in biologically and pharmaceutically active organic materials.[1] Sulfenylated heteroarenes can be found in molecules such as AZD4407, a 5-lipoxygenase inhibitor,[2] and thienoacene-based materials (Figure 1).[3] Pharmacological properties of Imidazopyridines are mainly dependent on the nature of the substituent's, and introduction of sulfenyl or selenyl groups on the aza-aromatic rings could impart marked biological properties to the compounds; for example, 3-sulfenyl indoles, 3-sulfenyl pyrroles, and 3-sulfenylimidazopyridines are of considerable therapeutic value against a variety of diseases.[4] 3-Sulfenylimidazopyridines are usually prepared by sulfenylation of imidazopyridines prior-synthesized. Direct formation of a C–S bond via C–H functionalization of heterocycles has received considerable attention in recent years. Thiols,[5] disulfides,[6] *N*-thioimides,[7] arylsulfonyl chlorides,[8] sulfonium salts[9] *etc*. have been used as the sulfenylating agents. The use of these reagents has some practical limitations such as thiols are foul-smelling, volatile, and toxic, where as disulfides are expensive, moisture sensitive and unstable. In addition, these methodologies suffer from some drawbacks like the use of a transition metal catalyst, stoichiometric amounts of oxidants and bases, harsh reaction conditions, and limited applicability.



a b

Fig. 1 Biologically active Sulfenylated heteroarenes; (a) 5-lipoxygenase inhibitor and (b) Inhibitor HIV-1 Integrase

Sulfonyl hydrazides are readily accessible and exist as stable solids, and they have been widely employed to form hydrazones and heterocycles which have versatile applications.[10] Moreover, sulfonyl hydrazides can be utilized as reductants[11] and sulfonyl sources[12] through the cleavage of their sulfur–nitrogen bonds, and very recently as aryl sources through the cleavage of their carbon–sulfur bonds.[13] Thus, it is highly desirable to develop an alternate method for the sulfenylation of imidazo[1,5-*a*]pyridines under transition metal free condition. Tian and coworkers first reported the thiolation of indoles employing sulfonyl hydrazides as a thiol surrogate.[14] Subsequently, Singh *et al*. also reported the synthesis of vinyl sulfides and diaryl thioethers using sulfonyl hydrazides under microwave irradiation.[15] Very recently Hajra and co-workers reported the thiolation of imidazo[1,2-*a*]pyridines using sulfonyl hydrazides.[16] So far, the use of sulfonyl hydrazides as sulfenylating agents is limited. Recently, we have reported a method for the synthesis of functionalized imidazopyridine derivatives employing novel method.[17] Based on our experiences on dithioesters[18] and inspired by Tian's pioneering work, we have envisaged that imidazo[1,5-*a*]pyridines could be sulfenylated at the 3-position under mild conditions. In continuation of our work on synthesis of heterocyclic compounds[19] herein, we report a new iodine-mediated convenient and tandem approach for the synthesis of 3-sulfenylimidazo[1,5-*a*]pyridines under mild conditions by sulfonyl hydrazides as a thiol surrogate in.

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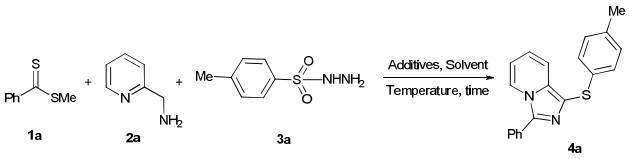
Table 1. Reaction optimization of **4a**[a]



No.	Additives	Solvent	Time in h	Temperature	Yield %
1	I_2 (1.0 eq)	Ethanol	12h	rt	-
2	I_2 (1.0 eq)	Ethanol	20 h	70 °C	48
3	I_2 (2.2 eq)	Ethanol	14 h	80 °C	87
4	I_2 (2.5 eq)	Ethanol	12 h	80 °C	86
5	I_2 (2.2 eq)	methanol	24 h	80 °C	75
6	I_2 (2.2 eq)	THF	24 h	80 °C	81
7	I_2 (2.2 eq)	DMF	24 h	80 °C	60
8	I_2 (2.2 eq)	CH_3CN	24 h	80 °C	78
9	I_2 (2.2 eq)	Ethyl acetate	20 h	80 °C	67
10	I_2 (2.2 eq)	$CHCl_3$	18 h	80 °C	55
11	I_2 (2.2 eq)	CH_2Cl_2	24 h	80 °C	30
12	TBAI(2.0eq)	Ethanol	24 h	80 °C	55
13	NIS (2.0 eq)	Ethanol	24 h	80 °C	43

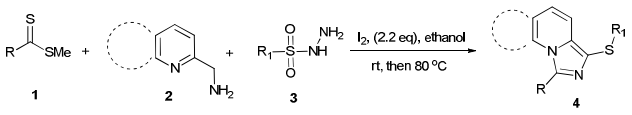
[a]Reactions were performed with 1.1 mmol of **1a** and 1.0 mmol of **2a**. Yields are isolated yields of chromatographically purified compounds

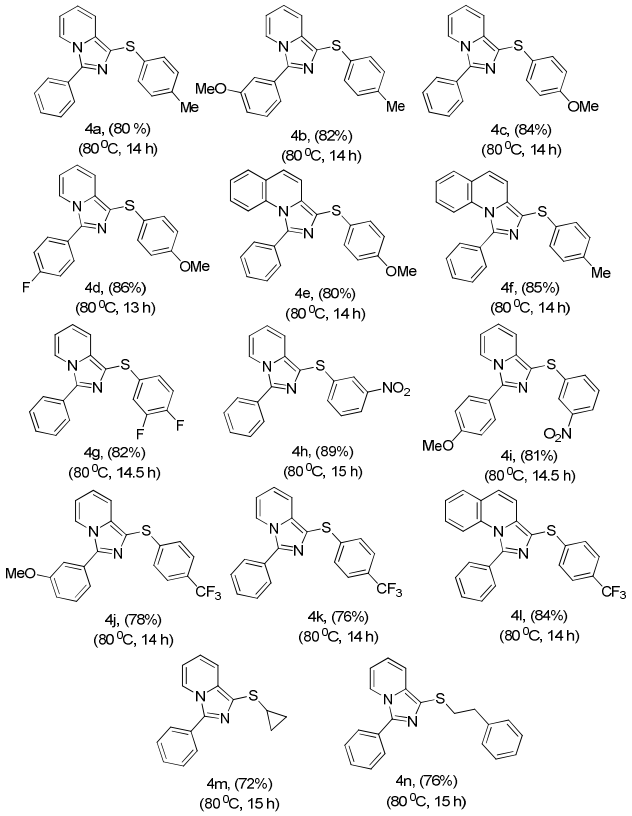
Result and discussion

We set out to identify the possible mild reaction conditions for the model reaction between 2-methylaminopyridine, *p*-toluenesulfonyl hydrazide and phenyl and results are listed in Table 1.

Initially the reaction was carried out using 1.0 eq of I_2 as an additive at room temperature. Gratifyingly, the 2-phenylimidazo[1,5-*a*]pyridine was obtained with 46% yield after 12 h. Inspired by this result, the reaction of *p*-toluenesulfonyl hydrazide, phenyl dithioester and 2-methylaminopyridine was stirred at 50 °C for 12 h which again formed 2-phenylimidazo[1,5-*a*]pyridine with 55% but failed to produce sulfonated product. The desired sulfonated product 3-sulfenylimidazo[1,5-*a*]pyridine was obtained in 48% yield when the temperature was raised to 70 °C (Table 1, entry 2). Optimisation of additive loading was carried out to improve the yield of **4a**. On increasing the additive loading to 2.2 eq, the desired product was obtained with 87% yield respectively (Table 1, entry 3). The additive failed to induce any positive impact on the yield with further enhancement of its amount to 2.5 eq (Table 1, entry 4). Thus the additive loading was optimized at 2.2 eq. The reaction was then performed in different common solvents like MeOH, THF, DMF, MeCN, ethyl acetate, $CHCl_3$, CH_2Cl_2 etc. (Table 1, entries 5–11). The better result was obtained in ethanol. Other iodide sources like TBAI and NIS were not as effective as I_2 (Table 1, entries 12 and 13). Thus the highest yield (87%) was obtained in the presence of 2.2 eq of I_2 in ethanol at 80 °C (Table 1, entry 3).

Scheme 1 Substrate scope for the synthesis of 3-sulfenylimidazo[1,5-*a*]pyridines





With the optimized reaction conditions in hand, the substrate scope was investigated and the results are shown in Scheme 1. Remarkable tolerance toward electronic demands of substituents on both dithioesters and *p*-toluenesulfonyl hydrazide were studied under optimized reaction conditions. Dithioesters bearing various substituents like –Me, –F at different positions on the benzene ring was efficiently reacted with *p*-toluenesulfonyl hydrazide to afford the desired products with high to excellent yields (**4a-4n**). Dithioesters with electron donating group (**4b** and **4j**) and electron withdrawing groups (**4d**) on the phenyl ring were well tolerated. The sulfonyl hydrazide bearing electron –donating groups (Me, O-Me) and electron withdrawing groups (F, NO_2 and CF_3) produced the desired product with high yields (scheme 1, **4g-4l**).

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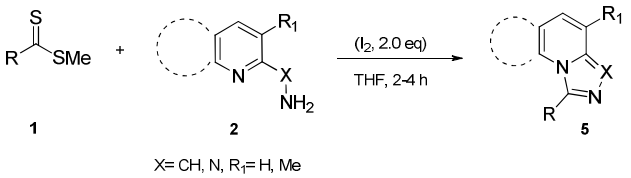
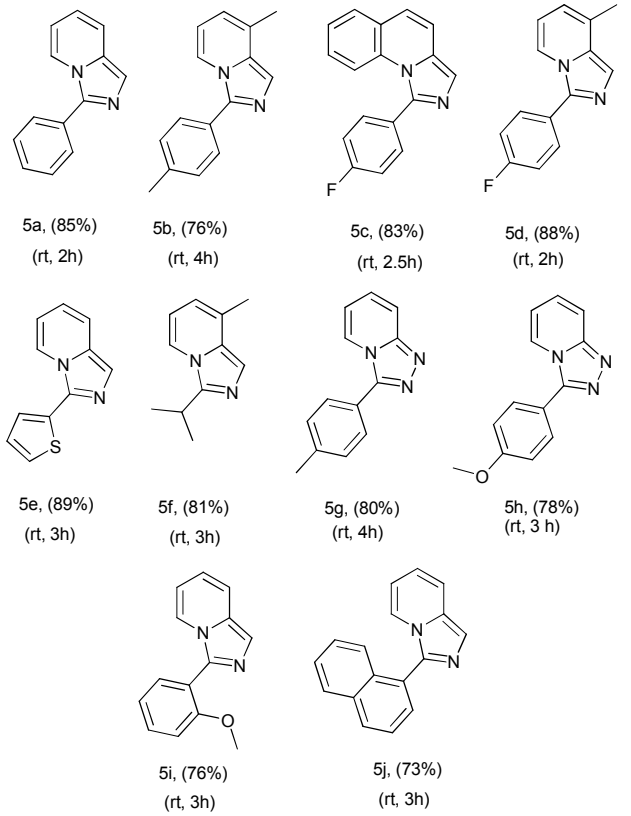
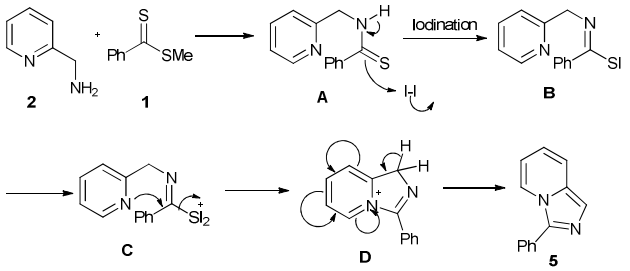
Scheme 2 Substrate scope for the synthesis of imidazolo[1,5-*a*]pyridines and [1,2,4]-triazolo[4,3-*a*]pyridines





The aliphatic sulfonyl hydrazides were successfully underwent the current reaction giving desired products under optimized reaction condition (scheme 1, **4m** and **4n**). The structure is also confirmed by single X-ray crystal studies for the compound **4h**.

To extend the scope of the methodology, a variety of dithioesters were allowed to react with 2- methylamino pyridine or hydrazine pyradine. Without the use of phenyl sulfonyl hydrazides, iodine mediated reaction of dithioesters and methylaminopyridine easily afforded the intermediate imidazo[1,5-*a*]pyridines without any oxidant. Number of protocols has been developed to synthesize imidazopyridines, [20-23] which suffers from disadvantages like the use of strong acidic, corrosive reagents such as $POCl_3$,[20a] $SOCl_2$,[20b] Lawesson's reagent[21a] and a modified Mitsunobu reaction.[21b] In contrast to the above methods, the present protocol provides a



Scheme 3 A plausible reaction mechanism for the formation of imidazolo[1,5-*a*]pyridines

novel method for the synthesis of imidazolopyridine in high yields under mild condition and simple work up procedures.

Insight of this and as result of great importance of functionalized imidazopyridines among natural and pharmaceutical products, we explored out a procedure with several kinds of substrates and the results are shown in Scheme 2.

A plausible mechanism for the the cyclization reaction leading to imidazolo[1,5-*a*]pyridines is displayed in scheme 3. The reaction of 2-methylaminopyridine **2** with phenyl dithioester **1** gives *N*-2-pyridylmethyl thioamide **A** followed by the iodination at sulfur generates intermediate **B**. Subsequent iodination again at sulfur takes place to form an electrophilic intermediate **C**, which undergoes intramolecular substitution by the pyridine nitrogen at the immino carbon to form **D**. Finally, the aromatization of D takes place to yield the product **5.**

Conclusions

An efficient I_2-mediated three-component reaction in one pot has been developed for the synthesis of 3-sulfenylimidazopyridines from dithioesters, 2-aminopyridines, and sulfonyl hydrazides. This tandem reaction process involves a C–H bond functionalization strategy for the formation of C–N and C–S bonds without any oxidants. The reaction proceeds through the cleavage of sulfur–nitrogen and sulfur–oxygen bonds by sulfonyl hydrazides as a thiol surrogate in. This methodology is applicable to both alkyl and aryl sulfonyl hydrazides, and various imidazopyridines having broad functionalities. Simple, one pot, broad substrate scope, transition metal free and mild reaction conditions are the attractive features of the present protocol. In addition, imidazopyridines can also be formed under the optimized reaction conditions without the use of disulfides.

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