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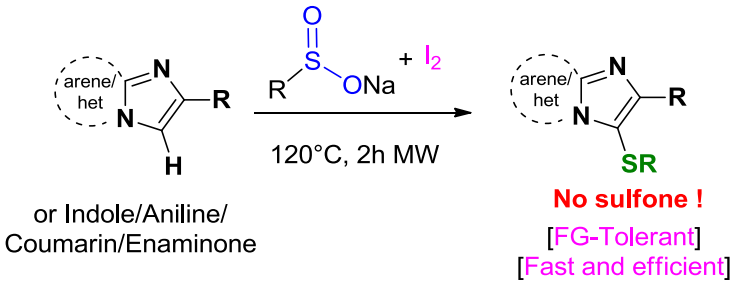

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Abstract An unprecedented I_2/sulfinate thiolating system is described for the sulfenylation of electron-rich heterocycles. This phosphine-free strategy enables simple, efficient and fast sulfenylation of imidazoheterocycles, aniline, indole, coumarine or enaminone.

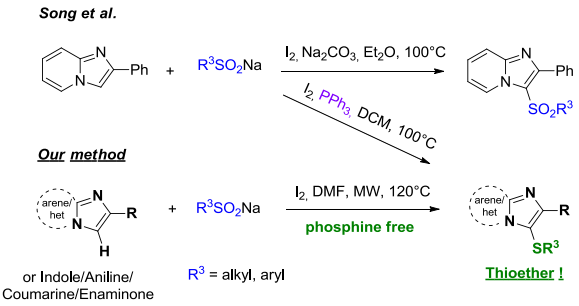
Key words sulfinate, iodine, microwave, heterocycles, thiolation.

Organic sulfur compounds, notably thioethers are prominent structural motifs in many bioactive natural products, pharmaceuticals, materials, and agrochemicals.[1] The classic method of synthesizing sulfides is from thiols or disulfides, but recently sulfinates have received wide attention. Sulfinate salts have versatile reactivity; the construction of sulfones, sulfonamides or thioethers.[2] These odorless and bench-stable reagents are commonly and easily prepared from thiol by oxidation or from sulfonyl chloride by reduction offering scope for a wide variety of approaches.

From sulfinates, thioether-generating methods based on electron-rich arenes were reported using an iodine source (NH_4I),[3] additives ($K_2S_2O_8$)[4] or iodine with acid or reducing agents.[5, 6, 7] Zhou *et al.* used ammonium iodide (NH_4I) for sulfenylation of imidazo[1,2-*a*]pyridines or flavones but needed harsh operating conditions (4 equiv. of iodine reagent, 135° for 20h).Similarly, Cao *et al.* described a radical thiolation from $K_2S_2O_8$/sulfinate to synthesize 3-arylthioindole for 24h.[4] From iodine and sulfinates, Deng *et al.* described sulfenylation of 2-napthols in acid conditions (HCOOH) after 24h at 100°C.[5] In 2018, Song *et al.* developed a difunctionalization of imidazopyridine using sodium sulfinates and iodine (Scheme 1).[6d] From base and iodine, they obtained only the sulfonylated product. Conversely, from iodine and reducing agent (PPh_3), they obtained only the sulfenylated product. Deng *et al.* used phosphites to deoxygenate sulfinates for 15h at 100°C to obtain 3-arylthioindole.[7]

Rendering such methods more attractive for industrial process, applications will mean making them fast, effective and robust.

Herein, we descibe an unprecedented thiolating system, I_2/sulfinate, enabling rapid and direct selective sulfenylation of electron-rich heterocycles, without any phosphine and in good to excellent yields.

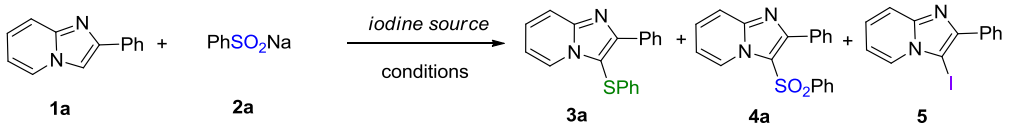


Scheme 1 Sulfuration of imidazo[1,2-*a*]pyridines from sulfinates and iodine.

We chose 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and sodium phenylsulfinate (**2a**) as the model substrates (see Table 1). Since our initial goal was the preparation of 3-phenylsulfonylated **4a**, Song's protocol was applied. However, reaction of **1a** and **2a** in Et_2O solvent under basic conditions at 100 °C for 20 h produced 3-phenylsulfonylated product **4a** in only 50% conversion and 50% 3-iodo compound **5** (Table 1, entry 1). We then tried acetonitrile, a solvent not mentioned by Song *et al.* Surprisingly, the same conditions led to the sulfenylated product **3a** in 54% conversion. Sulfonylated compound **4a** and iodo compound **5** were detected as minor product by LCMS (Table 1, entry 2).

Intrigued by this surprising result, we tested different solvents, temperatures and activators to determine whether the conversion into sulfenylated product could be increased. Microwave heating was chosen to reduce reaction times. Under the same conditions, one hour of reaction gives almost the same results (Table 1, entry 3). With another source of iodine (NaI), no product was detected (Table 1, entry 4). When the base was removed, the yield in terms of sulfenylation decreased slightly but the proportion of sulfone was halved, there was zero iodinated substrate (Table 1, Entry 5). This shows that the absence of base is beneficial. Of all the screened solvents, DMF was found to be the most suitable for this reaction (Table 1, entries 6-10). Increasing the time to 2h and the concentration to 1M led to an almost complete conversion with 87% yield after chromatography (Table 1, entry 12-13). Increasing the concentration to 2M did not improve the yield of **3a** either (Table 1, entry 14)

Table 1 Optimization of sulfenylation conditions[a,b]



1a 2a 3a 4a 5

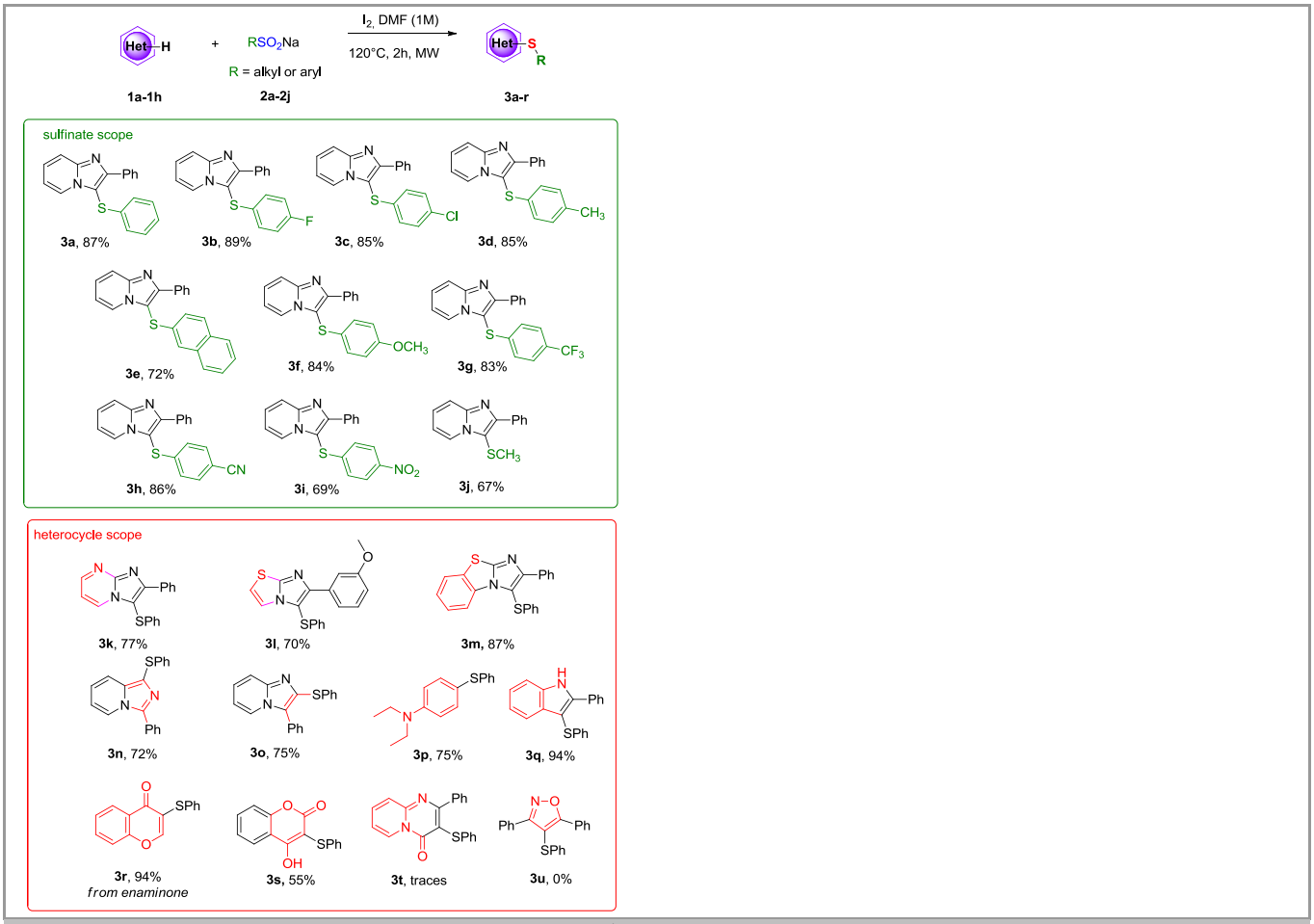
	Temperature/hour	Solvent	Iodine source (equiv.)	3a (%)[b]	4a (%)[b]	5 (%)[b]
1	100°C, 20h	Et_2O [0.1M] Na_2CO_3 (1.5)	I_2 (1.5)		50	50
2	100°C, 14h	ACN [0.1M] Na_2CO_3 (1.5)	I_2 (1.5)	54	11	12
3	120°C, 1h MW	ACN [0.1M] Na_2CO_3 (1.5)	I_2 (1)	53	26	21
4	120°C, 1h MW	ACN [0.1M] Na_2CO_3 (1.5)	NaI (1.5)	-	-	-
5	120°C, 1h MW	ACN [0.1M]	I_2 (1)	43	13	-
6	120°C, 1h MW	DMF [0.1M]	I_2 (1)	52	3	-
7	120°C, 1h MW	DMA [0.1M]	I_2 (1)	54	10	-
8	120°C, 1h MW	DMSO [0.1M]	I_2 (1)	43	1	-
9	120°C, 1h MW	Toluene [0.1M]	I_2 (1)	25	1	-
10	120°C, 1h MW	Glycerol [0.1M]	I_2 (1)	17	2	-
11	120°C, 1h MW	ACN [1M]	I_2 (1)	79	7	-
12	120°C, 1h MW	DMF [1M]	I_2 (1)	81	7	-
13	120°C, 2h MW	DMF [1M]	I_2 (1)	96 (87)	4	-
14	120°C, 1h MW	DMF [2M]	I_2 (1)	88	12	-

a) Reaction conditions: A mixture of imidazopyridine **1a** (0.2 mmol), phenyl sulfinate sodium **2a** (1 equiv.) and iodine source in solvent (0.2 mL) was heated in sealed tube.
b) LCMS yield of **3a** / **4a** (isolated yield).

Under the selected optimum conditions, we examined the effect of different arenesulfinates with electron-donating or electron-withdrawing groups on the aryl ring. It was found that theses arenesulfinates provided the desired products in high yields whatever the group. Only the strong electron-withdrawing group NO_2 in *para* position gave a slightly lower yield (**3i**, 69%). Similarly, the naphthyl group slightly decreased slightly efficiency (**3e**, 72%). In the presence of aliphatic sodium methanesulfinate (R = CH_3), the thioether was obtained in good yields (**3j**, 67%).

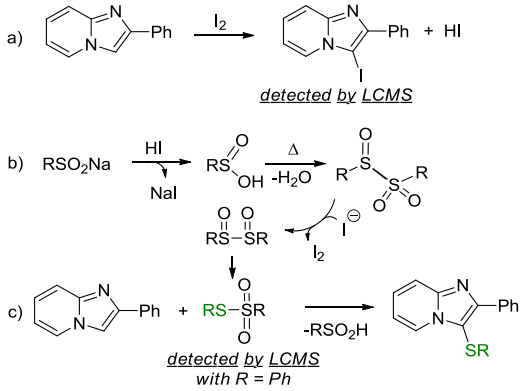
Subsequently, the substrate scope of the reaction was further extended to other electron-rich heterocycles. First, our protocol was successfully applied in imidazoheterocycle series (imidazo[1,2-*a*]pyrimidine **3k**, 77%) (imidazo[2,1-*b*]thiazole **3l**, 70%), (benzo[*d*]imidazo[2,1-*b*]thiazole **3m**, 87%, imidazo[1,5-*a*]pyridine **3n**, 72%). With imidazothiazole, the methoxy group in *meta* position of the phenyl did not affect the reactivity. For the first time, sulfenylation was performed at C2-position of imidazopyridine with a good

yield (**3o**, 75%) when the C3-position was blocked by a phenyl substituent. In aniline series, the same efficiency was obtained (**3p**, 75%). *N*-unprotected indole was also employed, affording product **3q** in 94% yield without sulfonylation of free-amine. From very reactive enaminone, excellent yield was obtained (**3r**, 94%). Conversely, moderate yield was observed with 4-hydrocoumarin (**3s**, 55%). Finally, our reaction conditions failed with less electron rich pyrimidin-4-one or isoxazole.



Scheme 2 Scope for thiolation with different sulfinates and heterocycles.[a,b] a) Reaction conditions: A mixture of heterocycles **1a-h** (1 mmol, 1 equiv.), sulfinate sodium **2a-j** (3 equiv.) and iodine (1 equiv.) in DMF (1 mL) was heated for 2 h at 120°C under microwave irradiations. b) Yield after column chromatography.

Based on relevant reports in the literature[2] and intermediates detected by LCMS, a plausible reaction mechanism for this sulfenylation is proposed in Scheme 3. Iodine could generate C3-iodination (detected by LCMS). By-product hydrogen iodide can convert sulfinates into sulfinic acid (RSO_2H) which could generate sulfinyl sulfone ($RS(O)SO_2R$) by heating and deshydratation.[8] Then iodide could reduce sulfinyl sulfone *into vic*-disulfoxide ($RS(O)S(O)R$) which could rearrange into thiosulfonate ($RSSO_2R$).[9] The formation of the species was confirmed by LCMS *in situ*. Finally, this excellent electrophilic moiety for sulfenylation could be trapped by imidazopyridines.



Scheme 3 Proposed mechanisms of the reaction.

In summary, we have developed method for the electrophilic substitution of electron-rich heterocycles from sodium aryl or alkylsulfinates and iodine.[10] The method affords good to excellent yields with excellent functional group tolerance and without using reducing agent or base. Moreover, microwave heating makes the procedure simple and fast.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(10) **General procedure for the thiolation** (**3a-3s**):
To a solution of heterocycle **1** (1 equiv.) in DMF (1 mL) in microwave vial, was added the appropriate sodium sulfinate **2** (3 equiv.) and iodine (1 equiv.). The vial was sealed and heated at 120°C by microwave irradiation for 2 hours. The solution was treated with a saturated $Na_2S_2O_3$ solution (10 mL) then the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried on Na_2SO_4, filtered and concentrated under vacuum to give the pure sulfinated product **3**.

2-phenyl-3-(phenylthio)imidazo[1,2-*a*]pyridine

White solid, yield: 262 mg (87%); mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27-8.29 (m, 1H), 8.20-8.22 (m, 2H), 7.75 (d, 1H), 7.42-7.46 (m, 2H), 7.33-.7.40 (m, 2H), 7.20-7.23 (m, 2H), 7.12-7.16 (m, 1H), 6.99-7.02 (m, 2H), 6.86-.6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.4, 147.2, 135.3, 133.3, 129.6 (2 x CH), 128.8, 128.6 (2 x CH), 128.5 (2 x CH), 126.9, 126.2, 125.7 (2 x CH), 124.7, 117.8, 113.3, 106.5, 106.7.