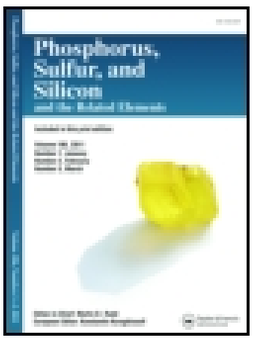

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One-pot synthesis of imidazo[1,2-α]pyridine thioethers using imidazo[1,2-α]pyridines, arylsulfonyl chlorides and hydrazine

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ABSTRACT

A one-pot reaction of making RS-substituted imidazo[1,2-α]pyridine derivatives by directly using aryl or alkylsulfonyl chloride and hydrazine was developed, selectively giving good yields of the expected products. Compared with previously reported methods of using $ArSO_2NHNH_2$ as a sulfur source, this method is much cheaper, more practical and convenient and enriches current methods to make thioether-containing compounds, providing a good example of green chemistry.

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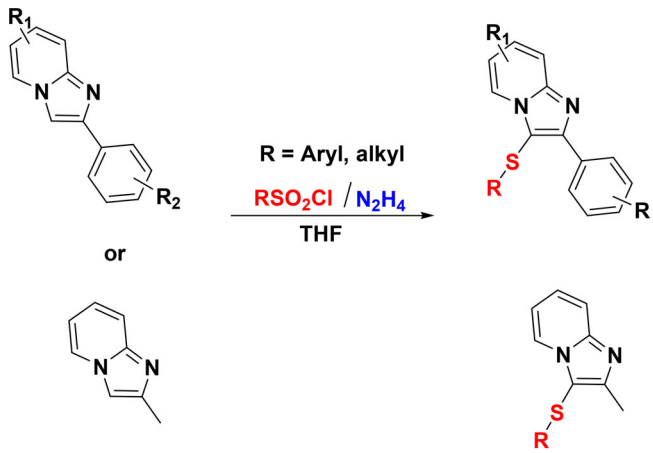
Imidazo[1,2-α]pyridine; sulfenylation; benzene sulfonylhydrazine; hydrazine

GRAPHICAL ABSTRACT



Introduction

Imidazo[1,2-α]pyridine structure is very important in drug discovery,[1] because its core is the same as the structures of several marketed drugs, such as Zolpidem and Alpidem. Imidazo[1,2-α]pyridine derivatives also possesses other important bioactivities,[2] such as antiviral,[3] antigout,[4] anticancer [5] and Alzheimer's disease.[6] Due to its importance in drug discovery, different methods of synthesizing imidazo[1,2-α]pyridine derivatives, particularly the synthesis of thioether derivatives, have been reported.[7] Several methods to make ArS- and MeS-substituted imidazo[1,2-α]pyridine derivatives have been reported.[8] Typically ArSSAr,[9] ArSH,[10] $ArSO_2NHNH_2$,[11] $ArSO_2Cl$[12] and Ar-SO_2Na[13] have been used as sulfenylation agents to make ArS- and MeS-substituted imidazo[1,2-α]pyridine derivatives in Scheme 1. Some of these methods involve using transition metal salts as catalysts, or toxic solvents. Although $ArSO_2NHNH_2$ has been reported to make ArS-substituted imidazo[1,2-α]pyridine derivatives before,[14] the method uses arylsulfonyl hydrazines as starting materials which are more expensive and less available than arylsulfonyl chlorides, so considerable room for improvements still exist.

Here, we report a more convenient method of directly using arylsulfonyl chloride and hydrazines instead of arylsulfonyl hydrazines to make ArS-substituted imidazo[1,2-α]pyridine derivatives. The reaction is carried out in THF with good product yields under environmentally friendly conditions.

Results and discussion

As arylsulfonyl chlorides can readily react with hydrazine to give arylsulfonyl hydrazines in good yields, so we plan to develop an one-pot three component reaction for directly making ArS-substituted imidazo[1,2-α]pyridine derivatives

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by using hydrazine, arylsulfonyls instead of using arylsulfonyl hydrazines in order to shorten reaction steps and simplify starting materials. To achieve this goal, a suitable reaction condition for this one-pot three component reaction need to be found.

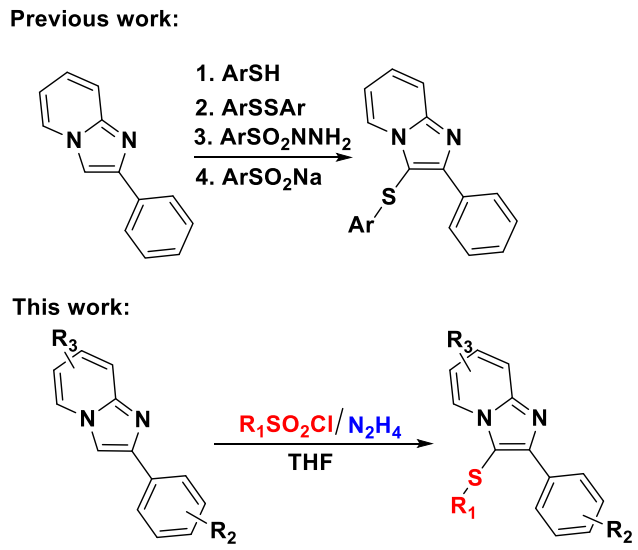
To screen for a suitable one-pot reaction condition for making ArS-substituted imidazo[1,2-α]pyridine with arylsulfonyl chloride and hydrazine as reactants, 2-phenylimidazo[1,2-α]pyridine **1a** was selected as a representative reactant, 4-methylbenzenesulfonyl chloride **2a** and hydrazine were used as the representative starting substrate materials. Different reaction conditions were employed in order to find out suitable reaction conditions. The experimental results are demonstrated in Table 1.

The screening reaction started with using DABCO as a base in THF solvent at 135 °C, but the reaction only gave a 35% yield of expected product **3a** (entry 1). Using Et_3N, Na_2CO_3, K_2CO_3 or $NaHCO_3$ as a base in THF at 135 °C generated **3a** in a 42%, 0%, 0% or 75% yield (entry 2, 3, 4, 5), repectively. Using different solvents such as DMF, THF, DMSO, EA or CH_3CN without a base involved at 135 °C, the reaction afforded **3a** in a 23%, 82%, 0%, 75% or 80% yield (entry 6, 7, 8, 9, 10), resepectively. While employing acetone or DCM generated **3a** in trace amount or 45% yield (entry 11, 12). Decreasing temperature from 135 °C to 115 °C reduced the reaction yield to 65% (entry 13). When the reaction temperature dropped to 90 °C, the reaction yield was only 43% (entry 14).

Based on the above screening, the optimized reaction conditions selected for the one-pot multicomponent reaction using arylsulfonyl chloride and hydrazine to generate ArS-substituted imidazo[1,2-α]pyridine derivatives are: imidazo[1,2-α]pyridine (1.0 equiv.), arylsulfonyl chloride (1.5 equiv.), hydrazine (3.0 equiv.) and THF as the solvent at 135 °C for 20 h.

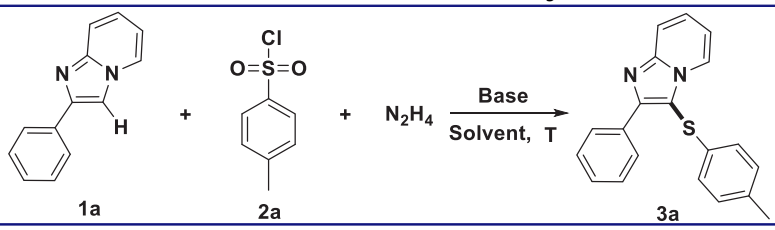
To further explore the scope of above reaction, several imidazo[1,2-α]pyridine reactants with electron-donating and electron-withdrawing functions were synthesized based on the reported methods in literature. Then in one pot these imidazo[1,2-α]pyridine analogs were reacted with hydrazine and different arylsulfonyl chloride with various functional groups on their benzene rings. Under the optimized condition found above, most reactions proceeded well, giving good yields of the regioselective ArS-subsituted imidazo[1,2-α]pyridine derivatives. The experimental results are shown in Table 2. Isolated yields of most reactions ranged from 54% to 88%. Selected alkyl sulfonyl chlorides were also tried for the reaction and gave good yields of the expected products of **3o**, **3p**, **3q**.

On the basis of the present investigations and previous reports on the reaction mechanism of imidazo[1,2-



Scheme 1. Previously reported synthetic methods versus our new method.

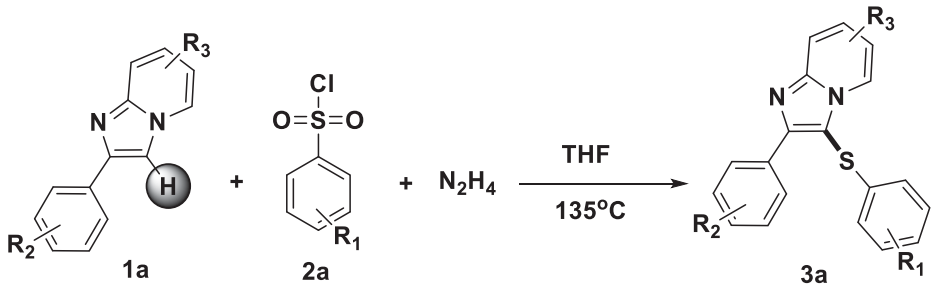
Table 1. Screening for suitable reaction conditions.[a]

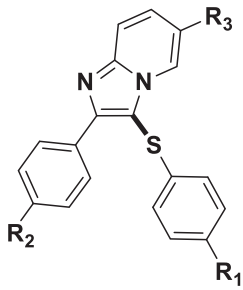


Entry	Base	Temp (°C)[b]	Solvent	Yield (%)[c]
1	DABCO	135	THF	35
2	Et_3N	135	THF	42
3	Na_2CO_3	135	THF	0
4	K_2CO_3	135	THF	0
5	$NaHCO_3$	135	THF	75
6	—	135	DMF	23
7	—	135	THF	82
8	—	135	DMSO	0
9	—	135	EA	75
10	—	135	CH_3CN	80
11	—	135	Acetone	trace
12	—	135	DCM	45
13	—	115	THF	65
14	—	90	THF	43

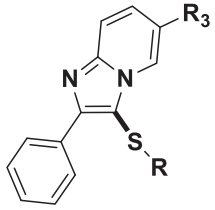
[a]Reaction conditions: imidazo[1,2-α]pyridine (0.5 mmol, 1.0 equiv.), sulfonyl chloride (1.5 equiv.), hydrazine (3.0 equiv.), solvent (0.5 mL) in sealed pressure tube.
[b]Reaction temperature: oil bath temperature.
[c]Isolated yield of **3a** was based on the reactant imidazo[1,2-α]pyridine **1a**. Reaction time: 20 h.

Table 2. Synthesis of RS-substituted imidazo[1,2-α]pyridine derivatives using different sulfonyl chloride.[a]

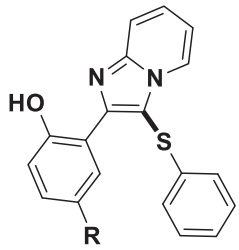




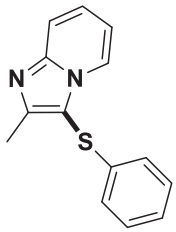
R_1= Me,	R_2 = H,	R3 = H,	3a	82%;
R_1= H,	R_2 = H,	R3 = H,	3b	88%;
R_1= OMe,	R_2 = H,	R3 = H,	3c	76%;
R_1= Cl,	R_2 = H,	R3 = H,	3d	75%;
R_1= Me,	R_2 = Cl,	R3 = H,	3h	87%;
R_1= H,	R_2 = OMe,	R3 = H,	3f	75%;
R_1= Br,	R_2 = H,	R3 = Me,	3i	76%;
R_1= Br,	R_2 = H,	R3 = Br,	3m	74%;
R_1= NO_2,	R_2 = H,	R3 = Me,	3j	74%;
R_1= H,	R_2 = Cl,	R3 = Me,	3k	76%;
R_1= Me,	R_2 = H,	R3 = Br,	3l	75%;



R = Me, R_3 = Me, 3o 82%;
R = Me, R_3 = H, 3p 75%;
R = Et, R_3 = H, 3q 76%;



R = H, 3e 87%;
Cl, 3g 80%;



3n 76%

[a]Reaction conditions: imidazo[1,2-α]pyridine (0.5 mmol, 1.0 equiv.), sulfonyl chloride (1.5 equiv.), hydrazine hydrate (3.0 equiv.), solvent (0.5 mL) in sealed pressure tube.
[b]Isolated yield of **3a** was based on the reactant imidazo[1,2-α]pyridine **1a**. Reaction time: 20 h.

α]pyridine with arylsulfonyl hydrazine,[15] a reaction mechanism is proposed in Scheme 2. Initially, aryl-or alkyl-sulfonyl chloride reacted quickly with hydrazine to afford sulfonyl hydrazine. Under heat, sulfonylhydrazine underwent the reaction to give reaction intermediate **A**, which reacted with imidazo[1,2-α]pyridine to give final product **3a**.

Experimental

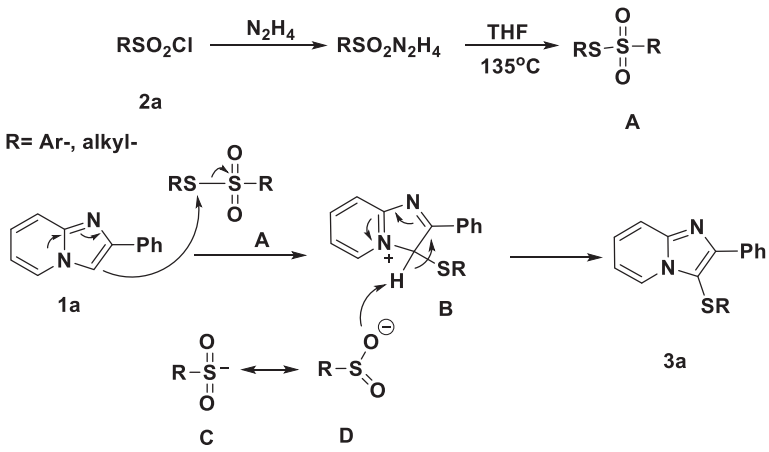
All reactions were carried out in sealed pressure tubes; stirring was achieved with an oven-dried magnetic stirring bar. Solvents were purified by standard methods unless otherwise noted. Commercially available reagents were purchased from Aladdin Company in China and used throughout without further purification other than those detailed below. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively. HRMS spectrometry (LC-HRMS) was recorded on a LXQ Spectrometer (Thermo Scientific) operating in the ESI-TOF mode (MeOH as a solvent). The Supplemental Materials contain sample ^{1}H and ^{13}C NMR spectra for the products 3 (Figures S1–S34).

General procedure for the synthesis of compounds 3a-q

Hydrazine (3.0 equiv.) was added to a pressure tube with THF (0.5 mL), sulfonyl chloride **2a** (1.5 equiv.) was added slowly under ice bath and stirred for 1 h. Then imidazo[1,2-α]pyridine **1a** (0.5 mmol, 1.0 equiv.) was added into and the mixture were stirred at 135 °C. After 20 h, the reaction was cooled down to room temperature, diluted with dichloromethane (2 mL), washed with brine (1 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (Petroleum ether: EtOAc =40:1) on silica gel to give the desired product **3a** as a colorless oil in an 82% yield.

2-Phenyl-3-(p-tolylthio)imidazo[1,2-α]pyridine (3a)[16a]

FTIR: 2979, 2927, 1343, 1090, 1461, 1050, 882 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.28 (tt,J = 7.0, 1.4 Hz, 3 H), 7.74



Scheme 2. A proposed reaction mechanism.

(dd, $J = 9.0$, 1.2 Hz, 1 H), 7.46 (dd, $J = 8.3$, 6.7 Hz, 2 H), 7.42 – 7.33 (m, 1 H), 7.29 (ddd, $J = 8.7$, 6.8, 1.3 Hz, 1 H), 7.02 (d, $J = 8.1$ Hz, 2 H), 6.99 – 6.89 (m, 2 H), 6.81 (td, $J = 6.8$, 1.2 Hz, 1 H), 2.25 (s, 3 H); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 151.20, 147.04, 136.05, 133.52, 131.54, 130.24, 128.59, 128.45, 128.42, 126.59, 125.85, 124.52, 117.61, 113.02, 106.87, 20.92. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{17}N_2S^+$ 317.1107 $(M+H)^+$, found 317.1105.

2-Phenyl-3-(phenylthio)imidazo[1,2-α]pyridine (3b)[16a]

FTIR:2979, 2923, 2338, 1591, 1466, 1047, 684 cm-1; **^{1}H-NMR**($CDCl_3$, 400 MHz): δ 8.15 (d, $J = 6.8$ Hz, 1 H), 8.11 (d, $J = 7.2$ Hz, 2 H), 7.63 (d, $J = 9.0$ Hz, 1 H), 7.33 (dd, $J = 8.3$, 6.6 Hz, 2 H), 7.21 (ddd, $J = 8.7$, 6.8, 1.3 Hz, 2 H), 7.09 (dd, $J = 8.3$, 6.7 Hz, 2 H), 7.02 (t, $J = 7.2$ Hz, 1 H), 6.92 – 6.86 (m, 2 H), 6.74 (t, $J = 6.8$ Hz, 1 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 151.41, 147.12, 135.18, 133.33, 129.46, 128.63, 128.44, 128.40, 126.72, 126.08, 125.58, 124.51, 117.64, 113.12, 106.34. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}N_2S^+$ 303.0950 $(M+H)^+$, found 303.0944.

3-((4-Methoxyphenyl)thio)-2-phenylimidazo [1,2-α]pyridine (3c)[16b]

FTIR: 3027, 2928, 2855, 1460, 1347, 1086, 798 cm^{-1}; **^{1}H-NMR**($CDCl_3$, 400 MHz): δ 8.34 (d, $J = 6.8$ Hz, 1 H), 8.26 (d, $J = 7.3$ Hz, 2 H), 7.77 (d, $J = 9.0$ Hz, 1 H), 7.48 (t, $J = 7.4$ Hz, 2 H), 7.44 – 7.33 (m, 2 H), 7.02 (d, $J = 8.8$ Hz, 2 H), 6.91 (td, $J = 6.8$, 1.1 Hz, 1 H), 6.81 – 6.75 (m, 2 H), 3.75 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 158.59, 150.59, 146.72, 133.19, 128.61, 128.43, 128.03, 126.71, 125.35, 124.49, 117.52, 115.17, 114.06, 113.12, 107.96, 55.34. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{17}N_2OS^+$ 333.1056 $(M+H)^+$, found 333.1048.

3-((4-Chlorophenyl)thio)-2-phenylimidazo[1,2-α]pyridine (3d)[16b]

FTIR: 3038, 2922, 2857, 1470, 1347, 1086, 692 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.27 (dt, $J = 6.8$, 1.2 Hz, 1 H), 8.24 – 8.16 (m, 2 H), 7.77 (dt, $J = 9.0$, 1.1 Hz, 1 H), 7.51 – 7.34 (m, 4 H), 7.25 – 7.16 (m, 2 H), 6.99 – 6.85 (m, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 151.61, 147.21, 133.74, 133.12, 132.07, 129.59, 128.77, 128.49, 128.32, 126.89, 126.84, 124.35, 117.78, 113.30, 105.73. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}ClN_2S^+$ 337.0561 $(M+H)^+$, found 337.0557.

2-(3-(Phenylthio)imidazo[1,2-α]pyridin-2-yl)phenol (3e)[16c]

FTIR: 3328, 3055, 3018, 2356, 1457, 1349, 1098, 734 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 13.13 (s, 1 H), 8.64 (dd, $J = 8.0$, 1.7 Hz, 1 H), 8.39 (dt, $J = 6.8$, 1.2 Hz, 1 H), 7.70 (dt, $J = 9.0$, 1.1 Hz, 1 H), 7.42 (ddd, $J = 9.0$, 6.8, 1.3 Hz, 1 H), 7.35 – 7.20 (m, 3 H), 7.20 – 7.14 (m, 1 H), 7.14 – 7.03 (m, 3 H), 6.96 (td, $J = 6.8$, 1.2 Hz, 1 H), 6.89 (ddd, $J = 8.3$, 7.2, 1.3 Hz, 1 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 158.44, 149.45, 144.66, 134.41, 130.63, 129.56, 127.75, 127.48, 126.39, 125.85, 124.24, 118.88, 117.73, 116.70, 116.13, 113.81, 105.47. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{15}N_2OS^+$ 319.0900 $(M+H)^+$, found 319.0904.

2-(4-Methoxyphenyl)-3-(phenylthio)imidazo[1,2-α] pyridine(3f)[16d]

FTIR: 2920, 2847, 2355, 1469, 1248, 1035, 744 cm^{-1}; **^{1}H-NMR**($CDCl_3$, 400 MHz): δ 8.27 (dt, $J = 6.9$, 1.2 Hz, 1 H), 8.24 – 8.17 (m, 2 H), 7.73 (dt, $J = 9.0$, 1.1 Hz, 1 H), 7.37 – 7.26 (m, 1 H), 7.26 – 7.17 (m, 2 H), 7.17 – 7.11 (m, 1 H), 7.04 – 6.95 (m, 4 H), 6.85 (td, J = 6.8, 1.2 Hz, 1 H), 3.85 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 160.02, 151.32, 147.08, 135.33, 129.66, 129.44, 126.59, 126.01, 125.95, 125.51, 124.42, 117.39, 113.87, 112.91, 105.31, 55.28. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{17}N_2OS^+$ 333.1056 $(M+H)^+$, found 333.1066.

5-Chloro-2-(3-(phenylthio)imidazo[1,2-α]pyridin-2-yl) phenol(3g)[16c]

FTIR: 3352, 2975, 2909, 1407, 1050, 881 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 13.15 (s, 1 H), 8.68 – 8.63 (m, 1 H),

8.41 – 8.37 (m, 1 H), 7.72 – 7.65 (m, 1 H), 7.43 (ddd, $J = 8.7$, 5.7, 1.3 Hz, 1 H), 7.30 – 7.14 (m, 4 H), 7.10 – 7.03 (m, 2 H), 7.03 – 6.92 (m, 2 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 157.12, 147.79, 144.50, 133.89, 130.29, 129.62, 127.71, 126.27, 124.25, 119.04, 118.27, 117.14, 116.77, 116.67, 114.04, 113.89, 106.44. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{14}ClN_2OS^+$ 353.0510 $(M+H)^+$, found 353.0516.

2-(4-Chlorophenyl)-3-(p-tolylthio)imidazo[1,2-α]pyridine (3h)[16b]

FTIR:3027, 2928, 2863, 1477, 1345, 1083, 786 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz):δ 8.30 (dt, $J = 6.8$, 1.2 Hz, 1 H), 8.25 – 8.15 (m, 2 H), 7.74 (dt, $J = 9.0$, 1.1 Hz, 1 H), 7.42 (d, $J = 8.6$ Hz, 2 H), 7.36 (ddd, $J = 9.0$, 6.8, 1.3 Hz, 1 H), 7.03 (s, 2 H), 6.91 (d, $J = 8.3$ Hz, 3 H), 2.28 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 149.81, 146.94, 136.27, 134.57, 131.83, 131.11, 130.28, 129.59, 128.64, 126.87, 125.87, 124.54, 117.59, 113.22, 107.16, 20.89. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}ClN_2S^+$ 351.0717 $(M+H)^+$, found 351.0721.

2-(4-Bromophenyl)-6-methyl-3-(phenylthio)imidazo[1,2-α]pyridine(3i)[16d]

FTIR: 3028, 2929, 2859, 1470, 1345, 1084, 796 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.22 – 8.12 (m, 2 H), 8.06 (d, $J = 1.5$ Hz, 1 H), 7.70 (d, $J = 9.1$ Hz, 1 H), 7.49 – 7.32 (m, 5 H), 7.25 (dd, $J = 9.1$, 1.7 Hz, 1 H), 6.88 (d, $J = 8.6$ Hz, 2 H), 2.36 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz):δ 151.17, 146.05, 134.67, 132.97, 132.49, 130.26, 128.73, 128.48, 128.22, 126.99, 123.42, 122.06, 119.77, 117.01, 105.09, 18.43. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}BrN_2S^+$ 395.0212$(M+H)^+$, found 395.0218.

6-Methyl-3-((4-nitrophenyl)thio)-2-phenylimidazo[1,2-α]pyridine (3j)[16d]

FTIR: 3023, 2921, 2837, 1467, 1337, 1079, 778 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz):δ 8.14 – 8.09 (m, 3 H), 8.02 (d, $J = 1.8$ Hz, 1 H), 7.76 (d, $J = 9.2$ Hz, 1 H), 7.49 – 7.36 (m, 3 H), 7.30 (d, $J = 12.7$ Hz, 2 H), 7.17 – 7.08 (m, 2 H), 2.37 (d, $J = 1.1$ Hz, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 146.4, 146.1, 145.1, 132.6, 130.7, 129.0, 128.6, 128.2, 125.2, 124.7, 124.5, 124.0, 121.8, 117.3, 103.2, 22.7. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}N_3O_2S^+$ 362.0958$(M+H)^+$, found 362.0962.

2-(4-Chlorophenyl)-6-methyl-3-(phenylthio)imidazo[1,2-α]pyridine (3k)[16d]

FTIR:3025, 2926, 2863, 1478, 1347, 1085, 786 cm^{-1};**^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.22 – 8.14 (m, 2 H), 8.09 (q, $J = 1.3$ Hz, 1 H), 7.65 (d, $J = 9.1$ Hz, 1 H), 7.44 – 7.36 (m, 2 H), 7.27 – 7.12 (m, 4 H), 7.03 – 6.95 (m, 2 H), 2.33 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 149.93, 146.12, 135.19, 134.44, 131.95, 130.07, 129.50, 129.47, 128.59, 126.11, 125.45, 123.20, 122.20, 116.97, 105.95, 18.39. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}ClN_2S^+$ 351.0717 $(M+H)^+$, found 351.0707.

6-Bromo-2-phenyl-3-(p-tolylthio)imidazo[1,2-α]pyridine (3l)[16d]

FTIR: 3028, 2928, 2869, 1477, 1349, 1080, 783 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.52 – 8.41 (m, 1 H), 8.26 – 8.19 (m, 2 H), 7.63 (dd, $J = 9.4$, 0.9 Hz, 1 H), 7.50 – 7.37 (m, 4 H), 7.07 (d, $J = 8.0$ Hz, 2 H), 6.97 – 6.91 (m, 2 H), 2.30 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 151.67, 145.38, 136.40, 132.91, 130.90, 130.35, 130.10, 128.83, 128.49, 128.32, 125.97, 124.69, 118.25, 107.96, 107.73, 20.91. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}BrN_2S^+$ 395.0212 $(M+H)^+$, found 395.0218.

6-Bromo-3-((4-bromophenyl)thio)-2-phenylimidazo[1,2-α]pyridine(3m)[16d]

FTIR: 3040, 2945, 2859, 1480, 1340, 1084, 692 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.42 (d, $J = 1.8$ Hz, 1 H), 8.18 (dd, $J = 8.2$, 1.6 Hz, 2 H), 7.50 – 7.41 (m, 4 H), 7.41 – 7.34 (m, 3 H), 6.89 (d, $J = 8.6$ Hz, 2 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 133.78, 132.66, 132.33, 130.56, 129.10, 128.59, 128.26, 127.74, 127.21, 124.51, 123.96, 120.24, 119.09, 118.37, 108.35. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{13}BrN_2S^+$ 458.9161 $(M+H)^+$, found 458.9167.

2-Methyl-3-(phenylthio)imidazo[1,2-α]pyridine (3n)[16d]

FTIR: 3041, 2925, 2849, 1483, 1341, 1083, 679 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.07 (dt, $J = 6.8$, 1.2 Hz, 1 H), 7.52 (dd, $J = 9.0$, 1.2 Hz, 1 H), 7.18 (ddd, $J = 8.7$, 6.8, 1.3 Hz, 1 H), 7.11 (dd, $J = 8.3$, 6.7 Hz, 2 H), 7.06 – 6.99 (m, 1 H), 6.89 – 6.80 (m, 2 H), 6.73 (td, $J = 6.8$, 1.2 Hz, 1 H), 2.50 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 150.65, 145.93, 134.57, 128.22, 124.97, 124.88, 124.60, 123.29, 115.96, 111.56, 106.34, 12.96. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{13}N_2S^+$ 241.0794 $(M+H)^+$, found 241.0798.

6-Methyl-3-(methylthio)-2-phenylimidazo[1,2-α]pyridine(3o)[16e]

FTIR: 3057, 2922, 2360, 1338, 818, 776 699 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz):δ 8.36 – 8.26 (m, 3 H), 7.60 (dd, $J = 9.1$, 0.9 Hz, 1 H), 7.53 – 7.46 (m, 2 H), 7.43 – 7.36 (m, 1 H), 7.17 (dd, $J = 9.1$, 1.8 Hz, 1 H), 2.43 (d, $J = 1.2$ Hz, 3 H), 2.28 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 148.50, 145.28, 133.87, 129.10, 128.35, 128.17, 128.15, 122.56, 122.02, 116.93, 110.96, 18.45, 18.23. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{15}N_2S^+$ 255.0950 $(M+H)^+$, found 255.0952.

3-(Methylthio)-2-phenylimidazo[1,2-α]pyridine(3p)[16e]

FTIR: 3066, 2922, 2364, 1345, 758, 695 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz):δ 8.50 (dt, $J = 6.9$, 1.2 Hz, 1 H), 8.34 – 8.26 (m, 2 H), 7.70 (dt, $J = 9.0$, 1.1 Hz, 1 H), 7.54 – 7.46 (m, 2 H), 7.44 – 7.37 (m, 1 H), 7.35 – 7.27 (m, 1 H), 6.96 (td, $J = 6.8$, 1.2 Hz, 1 H), 2.28 (s, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 148.74, 146.27, 133.72, 128.39, 128.30, 128.27, 126.01, 124.26, 117.60, 112.78, 111.44, 18.18. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{13}N_2S^+$241.0794 $(M+H)^+$,found 241.0792.

3-(Ethylthio)-2-phenylimidazo[1,2-α]pyridine(3q)[16f]

FTIR: 3064, 2922, 2364, 1345, 7563, 694 cm^{-1}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.55 (dt, $J = 6.8$, 1.2 Hz, 1 H), 8.40-8.31 (m, 2 H), 7.70 (dt, $J = 9.0$, 1.2 Hz, 1 H), 7.54-7.46 (m, 2 H), 7.45-7.37 (m, 1 H), 7.35-7.28 (m, 1 H), 6.94 (td, $J = 6.8$, 1.2 Hz, 1 H), 2.72 (q, $J = 7.4$ Hz, 2 H), 1.14 (t, $J = 7.4$ Hz, 3 H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 149.4, 146.3, 133.8, 128.3, 128.3, 128.2, 126.0, 124.4, 117.5, 112.7, 110.1, 29.9, 14.8. **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{15}N_2S^+$ 255.0950 $(M+H)^+$, found 255.0951.

Conclusion

In summary, a new one-pot reaction of making RS-substituted imidazo[1,2-α]pyridine derivatives by directly using aryl or alkylsulfonyl chloride and hydrazine was developed, giving good yields of expected products 3a-3q. Compared with previously reported methods of using $ArSO_2NHNH_2$ as sulfur sources, this method is much cheaper, flexible and convenient. This method is probably more suitable for a large scale production. Further studies to expand the scope of this methodology are under way.

Disclosure statement

There are no conflicts to declare.

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