Tetrahedron 67 (2011) 3690–3697

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient and clean CuI-catalyzed chalcogenylation of aromatic azaheterocycles with dichalcogenides

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ARTICLE INFO

Article history:
Received 17 January 2011
Received in revised form 20 March 2011
Accepted 22 March 2011
Available online 30 March 2011

Keywords:
Azaheterocycles
Dichalcogenides
Chalcogenylation
Copper(I) iodide
Air

ABSTRACT

A highly efficient and environmentally friendly method for catalytic chalcogenylation of imidazopyridines, imidazopyrimidines, indoles, and pyrrolo[2,3-*b*]pyridines with dichalcogenides has been developed by using CuI as catalyst under air. The reactions proceed smoothly to give the desired products in moderate to excellent yields, without the presence of other additive.

1. Introduction

Since the discovery of the potential utility of 3-sulfenylindoles as pharmaceuticals in 1993,[1] significant efforts have devoted to the development of new sulfenyl-substituted indoles and related compounds as well as their construction methods.[2–11,12a,b] Several efficient strategies for synthesis of 3-sulfenylindoles have been developed, including electrophilic substitution of indoles with sulfur-containing electrophiles, such as sulfenyl chloride,[2] *N*-thiophthalimides,[3] and quinone mono-*O*,*S*-acetals,[4] sulfoamination of 2-alkynylanilines with disulfides[5] or arylsulfenyl chlorides,[6] sulfanyl radical addition to alkynyl azides,[7] nucleophilic substitution of indole halides with metal mercaptides,[8] coupling reactions of indoles with disulfides and thiols in the presence of stoichiometric strong base.[9,10] Despite the synthetic utility of these transformations, most of these processes require the use of the strong bases, unavailable thiolating reagents or per-activated promoters, which are limited by undesired byproducts and are not suitable for sensitive substrates. In recent years, a few metal-catalyzed thiolations of heterocycles with thiols[11] and disulfides[12] have been developed. These reactions have proven to be extremely efficient for the synthesis of a wide variety of substituted sulfenylindoles and other heterocycles. Nonetheless, these catalytic variants are generally sensitive to the nature of heterocycles. For example, the presence of the strong electron-withdrawing substituent should prevent from the reaction; further, some additives are often required in order to achieve optimal yields and selectivity, which also limits the scope of these methods. On the other hand, despite the medicinal importance of sulfenyl-substituted azaheterocycles,[13,14] examples of discrete azaheterocycle species incorporating these functionalities remain scarce.

Imidazopyridines[15] and imidazopyrimidines[16] are one important class of alkaloids commonly found in natural products. Their biological activities have resulted in them often being used as building blocks in pharmaceutical compounds,[17,18] as ligands for transition metal catalysts.[19] In contrast to the ever-growing literature on sulfenyl- or selenyl-substituted indoles, examples of imidazopyridines and imidazopyrimidines incorporating these functionalities remain very scarce.[20] This is surprising, given the expectation that the introduction of sulfenyl or selenyl groups on the imidazole rings could impart markedly biological, chemical, and/or physical properties of the compounds for final application. There does not appear to be a large effort to expand upon this class of compounds, which is probably due to the lack of viable synthetic methodologies to access these compounds. Therefore, a new general and flexible approach to different classes of chalcogenyl-substituted heterocycles is highly desirable for the syntheses of delicate designed products. As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant carbo- and heterocyclic compounds,[21] we were interested in preparation of 3-chalcogenylimidazopyridines and 3-chalcogenylimidazopyrimidines by the direct thiolation of a C–H bond. We herein describe a general and

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doi:10.1016/j.tet.2011.03.067

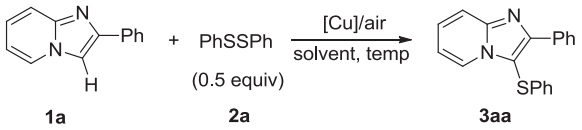
efficient method for catalytic chalcogenylation of imidazopyridines, imidazopyrimidines, indoles, and pyrrolo[2,3-*b*]pyridines with dichalcogenides in the presence of CuI and air under the neutral conditions.

2. Results and discussion

The reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with diphenyl disulfide (**2a**) was investigated to explore the optimal conditions, and the results are summarized in Table 1. Initially, a series of copper salts, including CuCl, CuBr, CuI, $Cu(OTf)_2$, $CuBr_2$, and $Cu(OAc)_2$ were screened under otherwise similar reaction conditions (Table 1, entries 1–6). We found that only copper(I) salts were active for catalytic thiolation of **1a** with **2a** (Table 1, entries 1–3), while divalent copper(II) salts, such as $Cu(OTf)_2$, $CuBr_2$, and $Cu(OAc)_2$, were ineffective, although small amounts of **3aa** were occasionally observed (Table 1, entries 4–6). The catalytic activity of monovalent copper(I) halide increases in order of CuI>CuBr>CuCl, which is contrast to the observation in the FeX_3/I_2 cocatalyzed thiolation of indoles with disulfides.[12b] To further optimize conditions with CuI as catalyst, we examined the effect of other reaction parameters. We quickly discovered that use of DMSO as solvent in place of DMF provided significantly improved yield (Table 1, entry 7), whereas non-coordinating solvents, such as 1,2-dichloroethane (DCE) and toluene, tend to shut down the reacting system (Table 1, entries 9 and 10). After conducting reactions in different temperatures, we arrived at much improved condition in which **3aa** was obtained in 88% yield when the reaction was carried out at 110 °C (Table 1, entry 8). It was noteworthy that air was also crucial for advancement of the reaction while the reaction under nitrogen (in the absence of oxygen) produced only a moderate yield (49%) of the product (Table 1, entry 11). In contrast to the observation in the CuI-catalyzed thiolation of benzoxazole with **2a**,[12c] wherein the additives of 2,2′-bipyridine and Cs_2CO_3 were required for a satisfactory yield, in the present case the presence of 2,2′-bipyridine as the ligand led to the decrease of the yield (Table 1, entry 12), and the presence of base also had an adverse effect on the reaction (Table 1, entry 13). The reaction was completed in 15 h at 110 °C and part of the product was decomposed in an extended reaction time (24 h) and/or at higher temperature (140 °C) (Table 1, entry 14). Moreover, the yield decreased to 63% (Table 1, entry 15) with the lower catalyst loading (5 mol %). The further investigation result indicated that no desired product could be formed in the absence of Cu-catalyst (Table 1, entry 16).

With the optimal protocol in hand, we subsequently explored the scope with respect to the imidazopyridines and imidazopyrimidines under the optimized conditions, and the results are shown in Table 2. The reaction of diphenyl disulfide **2a** with various imidazopyridines gave the corresponding 3-sulfenylimidazopyridines **3aa**–**3ia** in good to excellent yields (Table 2, entries 1–9). In general, the imidazopyridines bearing electron-donating groups were more reactive than those with electron-withdrawing groups (Table

Table 1
Optimization of reaction conditions for the formation of **3aa**[a]

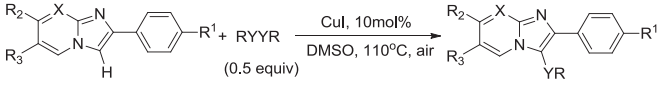


1a **2a** **3aa**

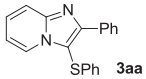
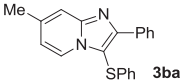
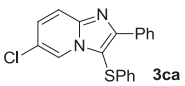
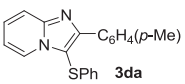
Entry	[Cu]	Solvent	Temp (°C)	Yield (%)[e]
1	CuCl	DMF	80	8
2	CuBr	DMF	80	37
3	CuI	DMF	80	50
4	$Cu(OTf)_2$	DMF	80	0
5	$CuBr_2$	DMF	80	26
6	$Cu(OAc)_2$	DMF	80	11
7	CuI	DMSO	80	73
8	CuI	DMSO	110	88
9	CuI	DCE	110	trace
10	CuI	Toluene	110	27
11[b]	CuI	DMSO	110	49
12[c]	CuI	DMSO	110	81
13	CuI/Cs_2CO_3	DMSO	110	71
14	CuI	DMSO	140	76
15[d]	CuI	DMSO	110	63
16		DMSO	110	0

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), [Cu] (0.02 mmol, 10 mol %), and solvent (2.0 mL) under air atmosphere for 15 h.
[b] Under N_2 atmosphere.
[c] 2,2′-Bipyridine (0.04 mmol, 20 mol %) was added.
[d] CuI (0.01 mmol, 5 mol %) was added.
[e] Isolated yield.

Table 2
CuI-catalyzed direct C–H chalcogenylation of **1** with dichalcogenide **2**[a]

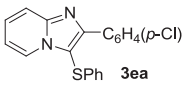
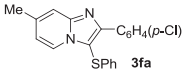
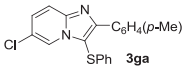
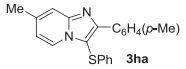
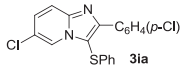
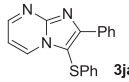
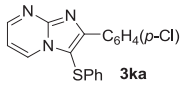
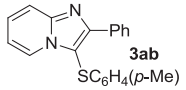
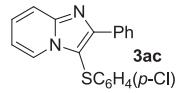
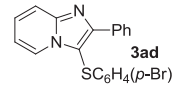
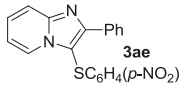
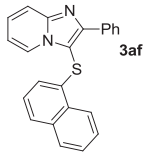
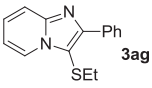
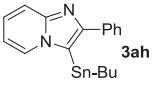
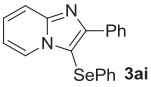
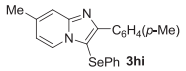
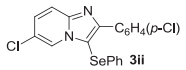
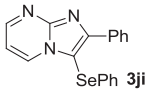


1 **2** **3**

Entry	**1**: R^1; R^2; R^3; X	**2**: RY	Product	Yield (%)[c]
1	**1a**: H; H; H; CH	**2a**: C_6H_5S	 **3aa**	88
2	**1b**: H; Me; H; CH	**2a**	 **3ba**	95
3	**1c**: H; H; Cl; CH	**2a**	 **3ca**	89
4	**1d**: Me; H; H; CH	**2a**	 **3da**	97

(*continued on next page*)

Table 2 (*continued*)

Entry	**1**: R^1; R^2; R^3; X	**2**: RY	Product	Yield (%)[c]
5	**1e**: Cl; H; H; CH	**2a**	 **3ea**	94
6	**1f**: Cl; Me; H; CH	**2a**	 **3fa**	91
7	**1g**: Me; H; Cl; CH	**2a**	 **3ga**	81
8	**1h**: Me; Me; H; CH	**2a**	 **3ha**	98
9	**1i**: Cl; H; Cl; CH	**2a**	 **3ia**	65
10	**1j**: H; H; H; N	**2a**	 **3ja**	76
11	**1k**: Cl; H; H; N	**2a**	 **3ka**	70
12	**1a**	**2b**: *p*-MeC_6H_4S	 **3ab**	89
13	**1a**	**2c**: *p*-ClC_6H_4S	 **3ac**	96
14	**1a**	**2d**:*p*-BrC_6H_4S	 **3ad**	93
15	**1a**	**2e**: *p*-$NO_2C_6H_4S$	 **3ae**	92
16	**1a**	**2f**: α-naphthyl	 **3af**	89
17[b]	**1a**	**2g**:EtS	 **3ag**	42
18[b]	**1a**	**2h**:*n*-BuS	 **3ah**	80
19	**1a**	**2i**:C_6H_5Se	 **3ai**	93
20	**1h**	**2i**	 **3hi**	95
21	**1i**	**2i**	 **3ii**	61
22	**1j**	**2i**	 **3ji**	66

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.10 mmol), CuI (0.02 mmol, 10 mol %), DMSO (2.0 mL), at 110 °C under air atmosphere for 10–18 h.
[b] Disulfide (0.20 mmol) was added.
[c] Isolated yield based on substrate **1**.

2, entries 8 and 9). For the reaction with substituted imidazopyrimidines **1j** and **1k**, the corresponding thiolation products **3ja** and **3ka** were also obtained in satisfactory yields (Table 2, entries 10 and 11). We also examined the scope with respect to disulfides. All the diaryl disulfides **2b**–**2f** with an electron-rich, electron-neutral, or electron-deficient substituent were screened, such as *p*-methyl, *p*-chloride, *p*-bromide, and α-naphthyl afforded the corresponding thioethers **3ab**–**3ad** and **3af** in excellent yields (Table 2, entries 12–14 and 16). It is noted that (p-$O_2NC_6H_4S)_2$ (**2e**), which is inactive in thiolation of benzoxazoles,[12c] displayed a high reactivity and reacted smoothly with **1a** to give the desired product in 92% yield (Table 2, entry 15). The structure of **3ae** was verified by X-ray diffraction analysis (Fig. 1).[26] Moreover, it was found that dialkyl disulfides **2g** and **2h** were also suitable substrates for the thiolation of imidazopyridine **1a** (Table 2, entries 17 and 18). Replacement of disulfide **2a** with diselenide **2i** as partner provided the desired products **3ai** and **3hi**–**3ji** in good to excellent yields (Table 2, entries 19–22).

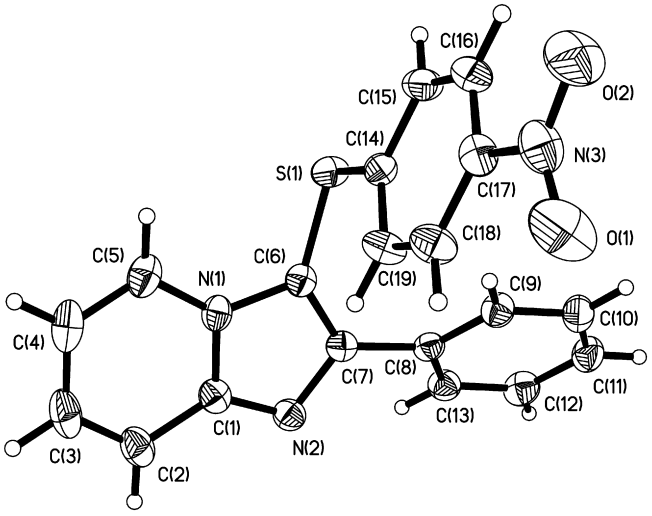
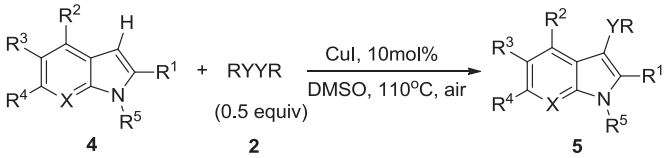


Fig. 1. Molecular structure of **3ae**.

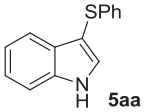
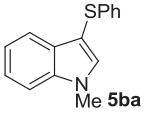
Having demonstrated the viability of the CuI-catalyzed thiolation of imidazopyridines and imidazopyrimidines with dichalcogenides, we decided to extend the new conditions to the thiolation of indoles. As shown in Table 3, the new reaction conditions described above are effective for the transformation of a number of different substrate combinations. The thiolation reactions of electron-rich (Table 3, entry 6), electron-neutral (Table 3, entries 2 and 3), and electron-deficient (Table 3, entries 7 and 8) *N*-alkylated indoles proceeded with good to excellent yields. In general, the *N*-alkylated indoles were more reactive than those without the substituent at the nitrogen atom. For example, starting materials **4a** and **4d**, which do not bear a protecting group at the nitrogen atom, provide the desired products **5aa** and **5da** in only moderate yields (Table 3, entries 1 and 4). This trend contrasts with that of previously described FeF_3/I_2-catalyzed reactions of indoles with disulfides, wherein the introduction of protecting groups at the N atom of indole rings results in the decrease of yields.[12b] To our delight, benzyl (Bn) protected pyrrolo[2,3-*b*]pyridine (**4i**) could also undergo the thiolation with **2a** in the presence of CuI and air, giving the desired coupling product in 85% yield (Table 3, entry 9). Moreover, it has been found that the Bn-protected indole is also a suitable substrate for the selenylation reaction (Table 3, entry 10). Reaction with dialkyl disulfide was also successful (Table 3, entry 11). Noticeably, the substrate bearing a carboxylate group at the 2-position of indole ring also gave the desired product in a satisfactory yield (Table 3, entry 12).[12b] The structure of **5ha** was determined by X-ray diffraction analysis (Fig. 2).[26] Finally, sulfenylation of the 3-substituted indoles with disulfide was evaluated under the standard reaction conditions. It was found that **4k** and **4l** reacted with **2a** to give the 2-sulfenylated products (Table 3, entries 13 and 14), indicating that the regioselectivity of sulfenylation is controllable. Consistent with the above observation in 3-sulfenylation, the *N*-protected indole **4l** provided the product in a higher yield compared with *N*-unprotected **4k**.

A plausible mechanism for the copper-catalyzed chalcogenylation of azaheterocycles with dichalcogenides is illustrated in Scheme 1.[22,2f] Initially, CuI reacts with **2** to form a RY^+ cation (**I**) as observed previously.[22a–c] Then the regioselectively electrophilic attack of **I** on imidazole ring results in the formation of substituted imidazolenium (**II**), which deprotonates to give the corresponding chalcogenated products **3** and the copper catalyst is regenerated. Clearly, the steric and electronic factors are favorable to the attack of RY^+ cation on the carbon atom at the 3-position, and the azaheterocycles bearing electron-donating groups are more reactive than those with electron-withdrawing groups. At the same time, the oxidation of the in situ generated RYH by air reproduces dichalcogenides **2**.

Table 3
CuI-catalyzed direct C–H chalcogenylation of indoles and pyrrolo[2,3-*b*]pyridine with dichalcogenide[a]

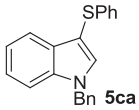
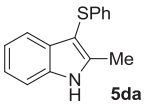
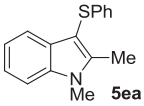
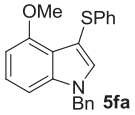
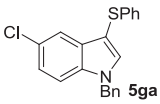
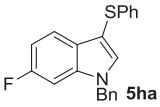
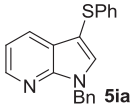
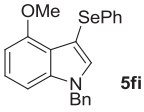
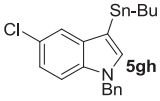
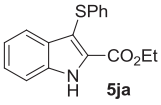
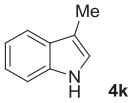
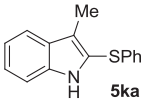
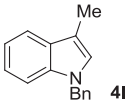
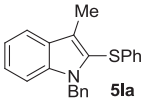


4 2 5

Entry	**4**: R^1; R^2; R^3; R^4; R^5; X	**2**: RY	Product	Yield (%)[c]
1	**4a**: H; H; H; H; H; CH	**2a**: C_6H_5S	 **5aa**	67
2	**4b**: H; H; H; H; Me; CH	**2a**	 **5ba**	84

(*continued on next page*)

Table 3 (*continued*)

Entry	**4**: R^1; R^2; R^3; R^4; R^5; X	**2**: RY	Product	Yield (%)[c]
3	**4c**: H; H; H; H; Bn; CH	**2a**	 **5ca**	93
4	**4d**: Me; H; H; H; H; CH	**2a**	 **5da**	41
5	**4e**: Me; H; H; H; Me; CH	**2a**	 **5ea**	80
6	**4f**: H; OMe; H; H; Bn; CH	**2a**	 **5fa**	96
7	**4g**: Bn; H; H; Cl; H; CH	**2a**	 **5ga**	98
8	**4h**: H; H; H; F; Bn; CH	**2a**	 **5ha**	92
9	**4i**: H; H; H; H; Bn; N	**2a**	 **5ia**	85
10	**4f**	**2i**	 **5fi**	84
11[b]	**4g**	**2h**	 **5gh**	72
12	**4j**: CO_2Et; H; H; H; H; CH	**2a**	 **5ja**	67
13	 **4k**	**2a**	 **5ka**	40
14	 **4l**	**2a**	 **5la**	83

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.10 mmol), CuI (0.02 mmol, 10 mol %), DMSO (2.0 mL), at 110 °C under air atmosphere for 10–18 h.
[b] Compound **2h** (0.20 mmol) was added.
[c] Isolated yield based on substrate **4**.

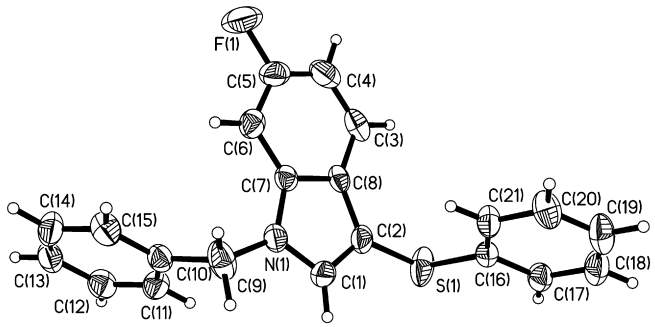
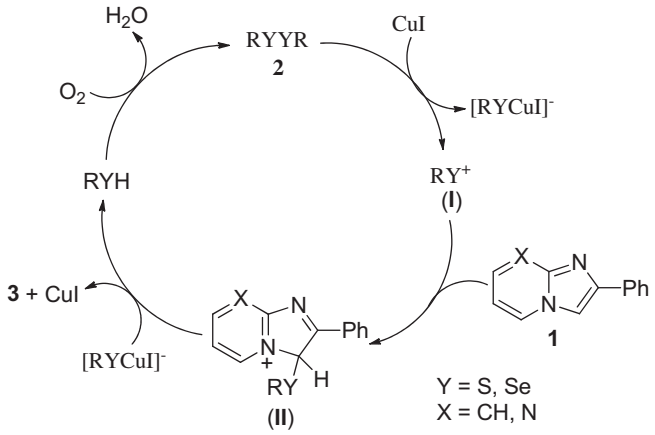


Fig. 2. X-ray structure of **5ha**.



Scheme 1. The possible reaction mechanism.

3. Conclusion

In summary, we have developed an efficient and atom economical method for synthesis of various chalcogenyl-substituted azaheterocycles, such as 3-chalcogenylimidazopyridines, 3-chalcogenylimidazopyrimidines, 3-chalcogenylindoles, and 3-chalcogenylpyrrolo[2,3-*b*]pyridines, by CuI-catalyzed chalcogenylation of the corresponding azaheterocycles with dichalcogenides. The simplicity, economy, high efficiency, and use of environmentally benign reagents render this method useful and competitive to the conventional approaches. Efforts to extend the applications of the transformation in organic synthesis as well as screen for biological activity of these types of compounds are currently underway in our laboratory.

4. Experimental section

4.1. General methods

All reactions were carried out in test tubes under air atmosphere. ^{1}H NMR spectra were recorded on a Bruker AVANCE ECA-400 MHz spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ=0 ppm) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were obtained by the same NMR spectrometers and were calibrated with $CDCl_3$ (δ=77.00 ppm). High-resolution mass spectra (HR-MS) were recorded using ESI ionization sources. Substrates **1**,[23] **2**,[24] and **4**[25] were prepared according to the reported methods. Methylsulfinylmethane (DMSO) was distilled under nitrogen from calcium hydride. Copper(I) iodide was purchased from Sigma–Aldrich. X-ray diffraction data for **3ae** and **5ha** (CCDC 784894, 784,895) were collected on a SMART APEX CCD diffractometer (graphite-monochromated Mo Kα radiation, Ŵ ϕ-ω-scan technique, λ=0.71073 Å). The intensity data were integrated by means of the SAINT program. SADABS was used to perform area-detector scaling and absorption corrections. The structures were solved by direct methods and were refined against F^2 using all reflections with the aid of the SHELXTL package. All non-hydrogen atoms were found from the difference Fourier syntheses and refined anisotropically. The H atoms were included in calculated positions with isotropic thermal parameters related to those of the supporting carbon atoms but were not included in the refinement. All calculations were performed using the Bruker Smart program.

4.2. General procedure for chalcogenylation of azaheterocycles with dichalcogenides

A mixture of azaheterocycles **1** or **4** (0.20 mmol), dichalcogenides **2** (0.10 mmol), and CuI (0.020 mmol, 10 mol %) in DMSO (2.0 mL) was stirred at 110 °C under air atmosphere for 10–18 h until complete consumption of staring material as monitored by TLC. The solution was then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with H_2O (3×10 mL), dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel (eluting with PE/EA=25/1 to 4/1) to afford the desired products **3** or **5**.

*4.2.1. 7-Methyl-2-phenyl-3-(phenylthio)H-imidazo[1,2-a]pyridine (**3ba**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, *J*=7.2 Hz, 2H), 8.10 (d, *J*=6.9 Hz, 1H), 7.47 (s, 1H), 7.41 (t, *J*=7.6 Hz, 2H), 7.34 (t, *J*=7.4 Hz, 1H), 7.18 (t, *J*=7.5 Hz, 2H), 7.10 (t, *J*=7.4 Hz, 1H), 6.97 (d, *J*=7.7 Hz, 2H), 6.65 (d, *J*=6.9 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.3, 147.5, 138.0, 135.6, 133.5, 129.5, 128.5, 128.4, 128.3, 126.0, 125.5, 123.7, 116.2, 115.7, 105.5, 21.5. HR-MS (ESI): calcd for $C_{20}H_{16}N_2S$ (M^++H): 317.1112, found: 317.1115.

*4.2.2. 6-Chloro-2-phenyl-3-(phenylthio)H-imidazo[1,2-a]pyridine (**3ca**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H), 8.19 (d, *J*=7.2 Hz, 2H), 7.65 (d, *J*=9.3 Hz, 1H), 7.42 (t, *J*=7.3 Hz, 2H), 7.36 (t, *J*=7.2 Hz, 1H), 7.26 (d, *J*=9.4 Hz, 1H), 7.21 (t, *J*=7.5 Hz, 2H), 7.13 (t, *J*=7.3 Hz, 1H), 6.99 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.2, 145.5, 134.6, 133.0, 129.7, 128.9, 128.6, 128.3, 128.1, 126.4, 125.7, 122.5, 121.6, 118.1, 107.4. HR-MS (ESI): calcd for $C_{19}H_{13}ClN_2S$ (M^++H): 337.0566, found: 337.0564.

*4.2.3. 3-(Phenylthio)-2-p-tolylH-imidazo[1,2-a]pyridine (**3da**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23 (d, *J*=6.7 Hz, 1H), 8.11 (d, *J*=8.1 Hz, 2H), 7.70 (d, *J*=9.0 Hz, 1H), 7.29 (d, *J*=7.0 Hz, 1H), 7.23 (d, *J*=7.3 Hz, 2H), 7.17 (t, *J*=7.6 Hz, 2H), 7.09 (t, *J*=7.6 Hz, 1H), 6.98 (d, *J*=7.3 Hz, 2H), 6.80 (t, *J*=6.7 Hz, 1H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.6, 147.1, 138.6, 135.3, 130.5, 129.5, 129.2, 128.3, 126.7, 126.1, 125.6, 124.5, 117.6, 113.080, 105.9, 21.4. HR-MS (ESI): calcd for $C_{20}H_{16}N_2S$ (M^++H): 317.1112, found: 317.1113.

*4.2.4. 2-(4-Chlorophenyl)-3-(phenylthio)H-imidazo[1,2-a]pyridine (**3ea**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.24 (d, *J*=6.4 Hz, 1H), 8.17 (d, *J*=8.4 Hz, 2H), 7.70 (d, *J*=8.9 Hz, 1H), 7.38 (d, *J*=7.4 Hz, 2H), 7.31 (t, *J*=9.0 Hz, 1H), 7.19 (t, *J*=7.1 Hz, 2H), 7.12 (t, *J*=7.7 Hz, 1H), 6.97 (d, *J*=7.3 Hz, 2H), 6.86–6.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.2, 147.1, 134.9, 134.6, 131.9, 129.6, 129.6, 128.7, 127.0, 126.3, 125.6, 124.6, 117.7, 113.3, 106.5. HR-MS (ESI): calcd for $C_{19}H_{13}ClN_2S$ (M^++H): 337.0566, found: 337.0551.

*4.2.5. 2-(4-Chlorophenyl)-7-methyl-3-(phenylthio)H-imidazo[1,2-a] pyridine (**3fa**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (d, *J*=8.5 Hz, 2H), 8.10 (d, *J*=6.9 Hz, 1H), 7.46 (s, 1H), 7.37 (d, *J*=8.5 Hz, 2H), 7.18 (t, *J*=7.6 Hz, 2H), 7.11 (t, *J*=7.2 Hz, 1H), 6.96 (d, *J*=7.9 Hz, 2H), 6.67 (d, *J*=7.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.0, 147.5, 138.3, 135.2, 134.5, 132.0, 129.5, 128.6, 126.2, 125.5, 123.7,

116.2, 115.9, 105.7, 21.5. HR-MS (ESI): calcd for $C_{20}H_{15}ClN_2S$ (M^++H): 351.0722, found: 351.0704.

*4.2.6. 6-Chloro-3-(phenylthio)-2-p-tolylH-imidazo[1,2-a]pyridine (**3ga**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.29 (s, 1H), 8.09 (d, J=8.1 Hz, 2H), 7.63 (d, J=9.4 Hz, 1H), 7.23 (d, J=7.6 Hz, 3H), 7.19 (d, J=7.7 Hz, 2H), 7.12 (t, J=7.2 Hz, 1H), 6.99 (d, J=7.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.3, 145.4, 138.9, 134.7, 130.1, 129.6, 129.3, 128.2, 127.9, 126.3, 125.7, 122.4, 121.5, 118.0, 106.9, 21.4. HR-MS (ESI): calcd for $C_{20}H_{15}ClN_2S$ (M^++H): 351.0722, found: 351.0714.

*4.2.7. 7-Methyl-3-(phenylthio)-2-p-tolylH-imidazo[1,2-a]pyridine (**3ha**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.08 (d, J=8.2 Hz, 3H), 7.46 (s, 1H), 7.23 (t, J=8.0 Hz, 2H), 7.17 (t, J=7.7 Hz, 2H), 7.09 (t, J=7.7 Hz, 1H), 6.97 (d, J=7.3 Hz, 2H), 6.64 (d, J=6.9 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.4, 147.5, 138.4, 137.9, 135.7, 130.7, 129.4, 129.2, 128.2, 125.9, 125.5, 123.7, 116.1, 115.6, 105.1, 21.4, 21.4. HR-MS (ESI): calcd for $C_{21}H_{18}N_2S$ (M^++H): 331.1269, found: 331.1262.

*4.2.8. 6-Chloro-2-(4-chlorophenyl)-3-(phenylthio)H-imidazo[1,2-a] pyridine (**3ia**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.66–8.64 (m, 1H), 8.52 (d, J=6.7 Hz, 1H), 8.29 (d, J=8.6 Hz, 2H), 7.40 (d, J=8.6 Hz, 2H), 7.22 (t, J=7.7 Hz, 2H), 7.15 (t, J=7.0 Hz, 1H), 6.98 (d, J=7.3 Hz, 2H), 6.96–6.93(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.9, 151.5, 150.0, 135.3, 133.9, 132.2, 131.2, 129.8, 129.7, 128.8, 126.7, 125.9, 109.6, 105.6. HR-MS (ESI): calcd for $C_{19}H_{12}Cl_2N_2S$ (M^++H): 371.0176, found: 371.0163.

*4.2.9. 2-(4-Chlorophenyl)-3-(phenylthio)imidazo[1,2-a]pyrimidine (**3ka**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (d, J=1.6 Hz, 1H), 8.15 (d, J=8.6 Hz, 2H), 7.64 (d, J=9.5 Hz, 1H), 7.39 (d, J=8.5 Hz, 2H), 7.28 (d, J=9.5 Hz, 1H), 7.22 (t, J=7.6 Hz, 2H), 7.16 (t, J=7.2 Hz, 1H), 6.98 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=150.9, 145.4, 134.9, 134.3, 131.4, 129.7, 129.5, 128.8, 128.4, 126.6, 125.7, 122.5, 121.8, 118.1, 107.4. HR-MS (ESI): calcd for $C_{18}H_{12}ClN_3S$ (M^++H): 338.0518, found: 338.0504.

*4.2.10. 3-(Naphthalen-1-ylthio)-2-phenylH-imidazo[1,2-a]pyridine (**3af**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25 (t, J=8.7 Hz, 3H), 7.76–7.67 (m, 3H), 7.55 (d, J=6.5 Hz, 1H), 7.44–7.36 (m, 6H), 7.31 (t, J=8.8 Hz, 1H), 7.16 (d, J=8.6 Hz, 1H), 6.80 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.6, 147.3, 133.9, 133.4, 132.7, 131.8, 129.3, 128.7, 128.5, 128.5, 127.8, 127.1, 126.9, 125.873, 124.6, 123.9, 123.5, 117.81, 113.2, 106.2. HR-MS (ESI): calcd for $C_{23}H_{16}N_2S$ (M^++H): 353.1112, found: 353.1103.

*4.2.11. 2-Phenyl-3-(phenylselanyl)H-imidazo[1,2-a]pyridine (**3ai**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.31 (d, J=6.8 Hz, 1H), 8.16 (d, J=7.5 Hz, 2H), 7.70 (d, J=9.0 Hz, 1H), 7.42 (t, J=7.3 Hz, 2H), 7.35 (t, J=7.5 Hz, 1H), 7.26 (t, J=6.9 Hz, 1H), 7.16–7.12 (m, 3H), 7.10–7.07 (m, 2H), 6.79 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.8, 147.8, 133.8, 130.9, 129.7, 128.8, 128.5, 128.4, 128.3, 126.7, 126.6, 125.7, 117.5, 113.1, 102.9. HR-MS (ESI): calcd for $C_{19}H_{14}N_2Se$ (M^++H): 351.0400, found: 351.0390.

*4.2.12. 7-Methyl-3-(phenylselanyl)-2-p-tolylH-imidazo[1,2-a]pyridine (**3hi**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.16 (d, J=6.9 Hz, 1H), 8.04 (t, J=8.1 Hz, 2H), 7.45 (s, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.15–7.12 (m, 3H), 7.08–7.06 (m, 2H), 6.62 (d, J=6.9 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.8, 148.1, 138.2, 137.6, 131.3, 131.1, 129.7, 129.1, 128.6, 128.1, 126.6, 124.7, 116.0, 115.5, 101.6, 21.4. HR-MS (ESI): calcd for $C_{21}H_{18}N_2Se$ (M^++H): 379.0713, found: 379.0709.

*4.2.13. 6-Chloro-2-(4-chlorophenyl)-3-(phenylselanyl)H-imidazo [1,2-a]pyridine (**3ii**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.63–8.58 (m, 2H), 8.25 (d, J=8.5 Hz, 2H), 7.41 (d, J=8.6 Hz, 2H), 7.19–7.17 (m, 3H), 7.10–7.08 (m, 2H), 6.94–6.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.7, 150.7, 135.1, 133.2, 131.6, 130.1, 130.0, 129.7, 128.7, 128.5, 127.3, 109.6, 101.9. HR-MS (ESI): calcd for $C_{19}H_{12}Cl_2N_2Se$ (M^++H): 418.9621, found: 418.9620.

*4.2.14. 2-Phenyl-3-(phenylselanyl)imidazo[1,2-a]pyrimidine (**3ji**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.60–8.56 (m, 2H), 8.28 (d, J=7.1 Hz, 2H), 7.44 (t, J=7.9 Hz, 2H), 7.38 (t, J=6.9 Hz, 1H), 7.17–7.15 (m, 3H), 7.11–7.08 (m, 2H), 6.91–6.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.0, 151.5, 150.8, 133.2, 133.1, 130.0, 129.9, 129.0, 129.0, 128.5, 128.4, 127.1, 109.5, 101.7. HR-MS (ESI): calcd for $C_{18}H_{13}N_3Se$ (M^++H): 352.0353, found: 352.0354.

*4.2.15. 1-Benzyl-4-methoxy-3-(phenylthio)-1H-indole (**5fa**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.23 (m, 4H), 7.16 (t, J=8.3 Hz, 5H), 7.10 (t, J=6.1 Hz, 3H), 7.02 (m, J=6.8 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 6.50 (d, J=7.8 Hz, 1H), 5.21 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.9, 141.0, 139.2, 136.8, 133.4, 129.0, 128.5, 128.0, 127.0, 126.4, 124.6, 123.8, 119.4, 103.5, 101.5, 101.3, 55.6, 50.5. HR-MS (ESI): calcd for $C_{22}H_{19}NOS$ (M^++H): 346.1265, found: 346.1263.

*4.2.16. 1-Benzyl-5-chloro-3-(phenylthio)-1H-indole (**5ga**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.58 (s, 1H), 7.37 (s, 1H), 7.28 (t, J=7.3 Hz, 3H), 7.18–7.04 (m, 9H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.1, 136.2, 135.9, 135.6, 131.3, 129.1, 128.9, 128.2, 127.0, 125.9, 125.1, 123.3, 119.4, 111.6, 101.4, 50.8. HR-MS (ESI): calcd for $C_{21}H_{16}ClNS$ (M^++H): 350.0770, found: 350.0746.

*4.2.17. 1-Benzyl-6-fluoro-3-(phenylthio)-1H-indole (**5ha**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.51–7.48 (m, 1H), 7.35 (s, 1H), 7.34–7.26 (m, 3H), 7.17–7.13 (m, 4H), 7.09–7.02 (m, 3H), 6.98 (d, J=9.6 Hz, 1H), 6.88 (t, J=8.8 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.6, 159.2, 139.2, 137.3, 136.2, 134.9, 129.1, 128.8, 128.2, 127.0, 126.4, 125.9, 125.0, 121.0, 120.9, 109.8, 109.5, 102.0, 97.1, 96.8, 50.7. HR-MS (ESI): calcd for $C_{21}H_{16}FNS$ (M^++H): 334.1065, found: 334.1053.

*4.2.18. 1-Benzyl-3-(phenylthio)-1H-pyrrolo[2,3-b]pyridine (**5ia**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.39 (d, J=6.2 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.44 (s, 1H), 7.33–7.27 (m, 3H), 7.22–7.02 (m, 8H), 5.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.4, 144.1, 143.1, 138.9, 137.0, 134.1, 128.9, 128.0, 127.6, 126.0, 125.1, 122.1, 117.0, 115.9, 100.6, 48.2. HR-MS (ESI): calcd for $C_{20}H_{16}N_2S$ (M^++H): 317.1112, found: 317.1119.

*4.2.19. 1-Benzyl-4-methoxy-3-(phenylselanyl)-1H-indole (**5fi**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (d, J=8.4 Hz, 2H), 7.24–7.22 (m, 2H), 7.15–7.06 (m, 8H), 6.88 (d, J=8.2 Hz, 1H), 6.50 (d, J=7.8 Hz, 1H), 5.20 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 139.1, 137.0, 135.1, 133.2, 129.9, 128.9, 128.9, 127.9, 127.0, 125.8, 123.6, 119.8, 103.4, 101.2, 95.7, 55.5, 50.5. HR-MS (ESI): calcd for $C_{22}H_{19}NOSe$ (M^++H): 394.0710, found: 394.0688.

*4.2.20. 1-Benzyl-3-(butylthio)-5-chloro-1H-indole (**5gh**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.73 (s, 1H), 7.30–7.27 (m, 2H), 7.23 (s, 1H), 7.17–7.06 (m, 6H), 5.24 (s, 2H), 2.66 (t, J=7.4 Hz, 2H), 1.54–1.47 (m, 2H), 1.43–1.34 (m, 2H), 0.86 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.6, 135.3, 134.5, 131.6, 129.0, 128.0, 126.8, 123.3, 122.8, 119.2, 111.3, 104.9, 50.5, 36.4, 32.0, 21.7, 13.8. HR-MS (ESI): calcd for $C_{19}H_{20}ClNS$ (M^++H): 330.1083, found: 330.1070.

Acknowledgements

We thank the NNSF of China, 973 program (2009CB825300), Shanghai Science and Technology Committee (No. 08dj1400100), the Research Fund for the Doctoral Program of Higher Education of

China, and Shanghai Leading Academic Discipline Project for financial support (B108).

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.067. These data include MOL files and InChIKeys of the most important compounds described in this article.

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26. CCDC 784894, 784895 for **3ae** and **5ha** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.