Accepted Manuscript

Mild ligand-free Cu^0-catalyzed chemoselective S-arylation of 2-mercaptoimidazole at low catalyst loading

Bryan Yong-Hao Tan, Yong-Chua Teo

PII: S0040-4020(16)30880-8

DOI: 10.1016/j.tet.2016.08.085

Reference: TET 28066

To appear in: *Tetrahedron*

Received Date: 11 April 2016

Revised Date: 17 August 2016

Accepted Date: 30 August 2016

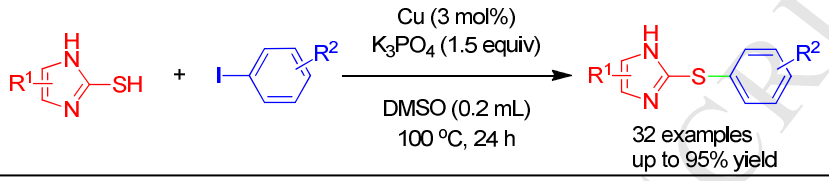
Please cite this article as: Tan BY-H, Teo Y-C, Mild ligand-free Cu^0-catalyzed chemoselective S-arylation of 2-mercaptoimidazole at low catalyst loading, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.08.085.

Graphical Abstract

Mild Ligand-free Cu^0-Catalyzed Chemoselective S-Arylation of 2-Mercaptoimidazole at Low Catalyst Loading

Leave this area blank for abstract info.

Bryan Yong-Hao Tan and Yong-Chua Teo *
Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616



Tetrahedron
journal homepage: www.elsevier.com

Mild ligand-free Cu^0-catalyzed chemoselective S-arylation of 2-mercaptoimidazole at low catalyst loading

Bryan Yong-Hao Tan and Yong-Chua Teo*

Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-mercaptoimidazole
ligand-free
chemoselective
S-arylation
Copper

ABSTRACT

A mild method for the Cu^0-catalyzed chemoselective C-S cross-coupling of 2-mercaptoimidazole derivatives with a series of with differently substituted iodobenzenes and iodothiophenes at 100 ºC is described. This method proceeds efficiently without ligands and at low catalyst loading (3 mol%), without the need for stringent inert conditions. Under optimized conditions, the S-arylated products were obtained in good yields of up to 90%.

1. Introduction

The S-arylmercaptoimidazole motif has been highlighted increasingly in medicinal chemistry literature, and can be predominantly found in compounds with antiviral,[1-3] anti-inflammatory,[4,5] antibacterial[6,7] and antitumor[8,9] properties. Among the few reported protocols, diphenyl sulfide[10,11] and aryl halides with the strong electron-withdrawing $–NO_2$ group[12,13] are typically used for their preparation. These reactions are not facile and require harsh conditions like the use of sodium hydride as base. Moreover, the presence of nucleophilic nitrogen in 2-mercaptoimidazole entails additional challenge in the synthesis. Therefore, an efficient method for the direct S-arylation of 2-mercaptoimidazole to access this important motif and its analogs will represent a significant advance to the synthetic community.

The transition metal-catalyzed C-S cross-coupling reaction has recently emerged as a powerful instrument for organic synthesis. Although challenges associated with the formation of disulfide bonds[14] and more crucially, the metal binding properties of organic sulfur compounds which in turn lead to catalyst poisoning,[15-17] have led to this class of reaction being less studied compared to its C-N and C-O counterparts, there has been considerable progress ever since the first S-arylation was achieved using a palladium catalyst in 1980.[18] In particular, copper-catalyzed Ullmann-type S-arylation reactions[19-25] caught our interest due to their relatively low toxicity, ease of handling as well as low cost[26,27] compared to the palladium-[16,17,28] and nickel-catalyzed[29-31] variants.

In spite of all these recent developments, catalytic methodologies for the S-arylation of 2-mercaptoimidazole remain elusive, with no successful C-S cross-coupling of 2-mercaptoimidazole and aryl halides being reported. Sambandam and co-workers demonstrated the cross-coupling between iodobenzene and 2-mercaptobenzimidazole through the use of CuI and 1,10-phenanthroline as assisting ligand.[32] However, this method lacks substrate scope and only worked with stabilized mercaptobenzimidazole substrates having strong electon-donating substitutents. The use of assisting ligand also adds additional cost to the methodology. Moreover, there are only three other reports that demonstrated cross-coupling reactions between sulfur-containing azoles with aryl halides.[33-35] In all instances, emphasis was conversely placed on the formation of more established diarylsulfides, with no examples of reaction between functionalized aryl halides and 2-mercaptoimidazole being described.

Therefore, we were motivated to channel our endeavor towards a facile and practical strategy for the synthesis of the above-mentioned S-arylmercaptoimidazole. However, the exsistence of thioketo and thiol tautomers in 2-mercaptoimidazole[36,37] will pose a potential challenge as both S- and N-arylation may take place. Given our prior experience in the development of practical and sustainable copper-catalyzed

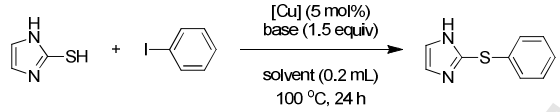
* Corresponding author. Tel.: +65 6790 3846; fax: +65 6896 9414; e-mail address: yongchua.teo@nie.edu.sg (Y.-C. Teo).

carbon-heteroatom cross-coupling reactions,[38-41] we envisage the application of such catalytic systems for this challenging transformation. We report herein the first Cu^0-catalyzed chemoselective S-arylation of 2-mercaptoimidazole with aryl and heteroaryl iodides. This mild ligand-free system affords excellent yields of the S-arylated derivatives (up to 90%) at low catalyst loadings (3 mol%), while the exclusion of stringent inert conditions exemplifies the simplicity and practicality of the protocol.

2. Results/Discussion

As an initial probe into the viability of such a chemoselective S-arylation reaction, 2-mercaptoimidazole and iodobenzene were used as model substrates. These two coupling partners were reacted in water at 100 ºC in the presence of 5 mol% CuI and 1.5 equivalents of anhydrous K_3PO_4, affording a yield of 20% even in ligand-free conditions (Table 1, entry 1). With this preliminary finding, we proceeded with our optimization stage with the screening of different bench-top organic solvents (entries 1–6). To our delight, good yields were obtained when polar aprotic solvents like DMF and DMSO were used as solvents respectively (entries 2 & 3). Next, the efficacy of different copper salts on the cross-coupling reaction was investigated. While CuCl, CuBr and Cu_2O have similar catalytic ability (entries 7–9), Cu^0 proved to be the best catalyst, affording the S-arylated product in an excellent yield of 84%, with no trace of regioisomers or polyarylated products being observed (entry 10). Control reactions carried out in the absence of Cu and base respectively illustrated that both are essential for the success of the protocol, with no intended product observed in either experiments (entries 11 & 12). The impact which different bases have on the reaction efficiency was subsequently investigated (entries 13–17). Although the use of different bases did not alter chemoselectivity, lower yield was detected. To improve atom efficiency and practicality, catalyst loading and reaction temperature were consequently lowered (entries 18–20). We are pleased to report that there was no reduction in yield when the catalyst loading was lowered to a mere 3 mol% (entry 18). In summary, the chemoselective S-arylation of 2-mercaptoimidazole in DMSO was accomplished through a combination of Cu^0 (3 mol%) and anhydrous K_3PO_4 (1.5 equiv), stirring the mixture under air at 100 ºC for 24 h.

Table 1. Optimization studies on the Cu-catalyzed cross-coupling of 2-mercaptoimidazole and iodobenzene.[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	K_3PO_4	water	20
2	CuI	K_3PO_4	DMF	81
3	CuI	K_3PO_4	DMSO	84
4	CuI	K_3PO_4	Dioxane	12
5	CuI	K_3PO_4	THF	10
6	CuI	K_3PO_4	Toluene	0
7	CuCl	K_3PO_4	DMSO	79
8	CuBr	K_3PO_4	DMSO	80
9	Cu_2O	K_3PO_4	DMSO	82
10	Cu	K_3PO_4	DMSO	84
11	-	K_3PO_4	DMSO	0
12	Cu	-	DMSO	0
13	Cu	K_2CO_3	DMSO	73
14	Cu	KOH	DMSO	78
15	Cu	Cs_2CO_3	DMSO	80
16	Cu	CsOAc	DMSO	70
17	Cu	KO^{t}Bu	DMSO	45
18	Cu	K_3PO_4	DMSO	84[c]
19	Cu	K_3PO_4	DMSO	40[d]
20	Cu	K_3PO_4	DMSO	70[c,e]

[a]Reaction conditions: Cu catalyst (5 mol%), base (0.75 mmol), 2-mercaptoimidazole (0.50 mmol), solvent (0.2 mL), iodobenzene (0.75 mmol), 100 ºC for 24 h in air.

[b]Isolated yield.

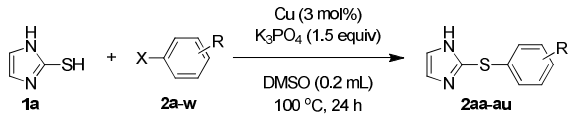
[c]3 mol% Cu used.

[d]1 mol% Cu used.

[e]Reaction carried out at 90 ºC.

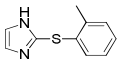
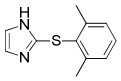
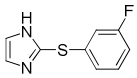
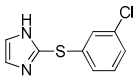
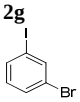
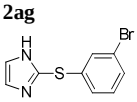
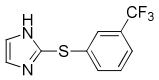
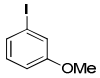
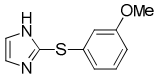
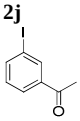
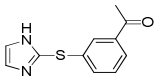
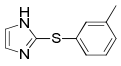
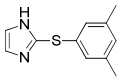
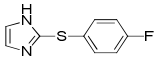
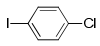
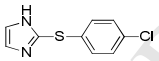
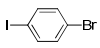
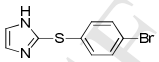
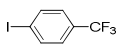
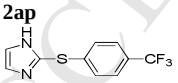
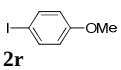
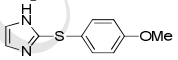
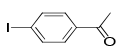
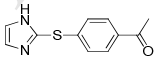
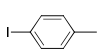
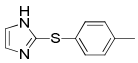
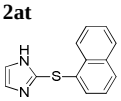
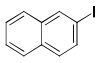
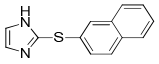
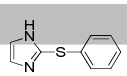
With the optimal conditions in hand, we demonstrated the generality of the protocol through the coupling of 2-mercaptoimidazole with a variety of electron-rich and electron-poor aryl iodides (Table 2, entries 1–22). In general, good to excellent yields (60–89%) were observed, and we are pleased to disclose that most of the desired products obtained in this table are new, with no prior synthesis recorded by other protocols. Despite the possible hindrance to the reaction due to steric repulsion, a common phenomenon seen in our previously reported cross-coupling reactions,[42,40,43,44] good to excellent yields (up to 82%) were still achieved for *ortho*-substituted aryl iodides (entries 2–5). This is likely due to the bigger size of the sulfur atom compared to nitrogen, hence able to better tolerate the steric hindrance.[45] In addition, 2-mercaptoimidazole reacted readily with various *meta*- and *para*-substituted iodobenzenes, regardless of the electronic nature, to give the corresponding products **2af**–**av** in good to excellent yields (entries 6–22). Notably, a representative base-sensitive enolizable ketone substituent was well-tolerated by the protocol affording the product in a good yield of 84% (entry 11). However, reactions did not proceed when iodobenzene with strongly basic and acidic substituents were employed. This is a common phenomenon observed in many Ullmann-type carbon-heteroatom bond formation reactions.[46-49] Another potential drawback of the protocol is the low reactivity when bromobenzene was used as the electrophile, affording a low yield of 20% (entry 23).

Table 2. Chemoselective S-arylation of 2-mercaptoimidazole with various substituted aryl halides.[a]



Entry	ArX	Product	Yield (%)[b]
1	**2a**	**2aa**	84
2	**2b**	**2ab**	71
3	**2c**	**2ac**	76

Table 2. (continued)

Entry	ArX	Product	Yield (%)[b]
4	 **2d**	 **2ad**	82
5	 **2e**	 **2ae**	60
6	 **2f**	 **2af**	80
7	 **2g**	 **2ag**	80
8	 **2h**	 **2ah**	80
9	 **2i**	 **2ai**	82
10	 **2j**	 **2aj**	81
11	 **2k**	 **2ak**	84
12	 **2l**	 **2al**	81
13	 **2m**	 **2am**	80
14	 **2n**	 **2an**	83
15	 **2o**	 **2ao**	89
16	 **2p**	 **2ap**	84
17	 **2q**	 **2aq**	82
18	 **2r**	 **2ar**	81
19	 **2s**	 **2as**	88
20	 **2t**	 **2at**	85
21	 **2u**	 **2au**	70
22	 **2v**	 **2av**	80
23	 **2w**	 **2aa**	20

[a]Reactions were carried out with Cu (3 mol%), K_3PO_4 (0.75 mmol), 2-mercaptoimidzole (0.50 mmol), DMSO (0.2 mL), substituted iodobenzene (0.75 mmol), 100 ºC for 24 h in air.

[b]Isolated yield.

Motivated by the positive results above, we proceeded to explore the possible chemoselective cross-coupling of heteroaryl halides with 2-mercaptoimidazole, as shown in Table 3. Indeed, S-arylation for a range of iodothiophenes afforded good to excellent yields of up to 85% (Table 3, entries 1–4). Regrettably, similar to our observations with bromobenzene (Table 2, entry 23), both 2- and 3-bromothiophene were not reactive enough for successful heteroarylation (entries 5 & 6). Furthermore, attempts with various iodopyridines as the coupling partner were not conclusive as the products obtained from the reactions could not be adequately characterized.

Table 3. Chemoselective S-arylation of 2-mercaptoimidazole with substituted iodoheterocycles.[a]

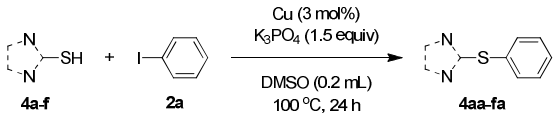
Entry	Het-X	Product	Yield (%)[b]
1	**3a**	**3aa**	60
2	**3b**	**3ab**	85
3	**3c**	**3ac**	62
4	**3d**	**3ad**	70
5	**3e**	**3aa**	15
6	**3f**	**3ab**	17

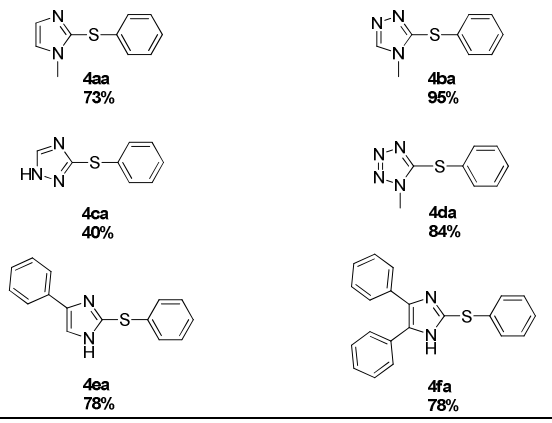
[a]Reactions were carried out with Cu (3 mol%), K_3PO_4 (0.75 mmol), 2-mercaptoimidzole (0.50 mmol), DMSO (0.2 mL), substituted heterocycles (0.75 mmol), 100 ºC for 24 h in air.

[b]Isolated yield.

Next, we focused our attention on broadening the scope of the methodology by applying it on a series of mercaptoazoles. The results are summarized in Table 4, where moderate to excellent yields of up to 95% were obtained. Particularly, we were able to obtain a good yield of 73% of **4aa**, formed by the cross-coupling of iodobenzene and 2-mercapto-1-methylimidazole. This reaction, achieved using the *N*-methyl derivative of 2-mercaptoimidazole.

Table 4. Chemoselective S-arylation of sulfur-containing azoles with iodobenzene.[a]

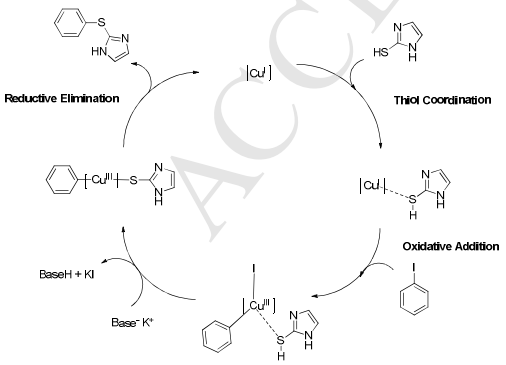




[a]Isolated yields for reactions carried out with Cu (3 mol%), K_3PO_4 (0.75 mmol), azoles (0.50 mmol), DMSO (0.2 mL), iodobenzene (0.75 mmol), 100 ºC for 24 h in air.

While the mechanism of copper-catalyzed cross-coupling reactions has not been fully determined, based on the reported literature,[50,51] as well as observations made throughout our study; firstly, all Cu salts screened were efficient catalysts for the reaction (Table 1, entries 1, 7–9), and secondly, solid Cu^0 was not observed at the end of every reaction, we postulate that the mechanism involves three elementary steps. The first step begins with the coordination of 2-mercaptoimidazole to the Cu^I metal center, formed through the oxidation of Cu^0 by DMSO, a well-known oxidant.[52-54] Next, an oxidative addition of the iodobenzene to the catalyst, and lastly, the regeneration of the Cu catalyst after a reductive elimination of the S-arylated product.

Scheme 1. Proposed mechanism for the selective S-arylation of 2-mercaptoimidazole with iodobenzene.



3. Conclusions

In summary, a mild protocol which requires only a low 3 mol% of Cu^0 catalyst is developed for the chemoselective S-arylation of 2-mercaptoimidazole with differently substituted iodobenzenes and iodothiophenes. This method has shown good efficiency, tolerating aryl iodides of various electronic and steric properties to give us access to a large number of new compounds that were not previously synthesized. The experimental simplicity of this catalytic system, which does not require the addition of assisting ligands and inert conditions, is expected to be particularly useful in industrial applications and the development of therapeutics.

4. Experimental section

4.1. General Methods

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Flash chromatography was performed using Merck silica gel 60 with AR grade solvents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of DMSO-d_6 (δ 2.500, quintet). Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of DMSO-d_6 (δ 39.51, septet). Mass spectroscopy was performed using Agilent 1100 series LC/MSD.

All reagents were purchased from commercial supplier and were used without any purification. Copper powder was purchased from Sigma Aldrich.

4.2. General procedure for S-aryl/heteroarylation of 2-mercaptoimidazole/Sulfur-containing azoles.

A mixture of Cu^0 powder (Sigma-Aldrich, <425 μm, 99.5% trace metals basis, 0.095 mg, 0.015 mmol, 3-mol%), anhydrous K_3PO_4 (0.75 mmol), 2-mercaptoimidazole/sulfur-containing azoles (0.5 mmol), DMSO (0.2 mL) and aryl halide (0.75 mmol) were added to a reaction vial and a screw cap was fitted to it. The reaction mixture was stirred under air in a closed system at 100 ºC for 24 h. The heterogeneous mixture was subsequently cooled to room temperature and diluted with 4.0 mL dichloromethane. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was loaded onto the column using minimal amounts of dichloromethane and was purified by silica-gel column chromatography to afford the *S*-arylated product. The identity and purity of products was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

4.3. NMR Data for Products

2-(phenylthio)-1*H*-imidazole (2aa) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 74 mg (84% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 102-104 ºC. R_f = 0.46 (50% hexane/EtOAc). ν_{max} = 3047, 3001, 2700, 2542, 1860, 1550, 1310, 1211, 1087, 1020 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.74 (bs, 1H, NH), 7.31 (t, *J* = 7.6 Hz, 2H, Ph), 7.23-7.18 (m, 3H, Ph), 7.12 (d, *J* = 8.1 Hz, 2H, CHCH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 135.9,

134.5, 129.3, 127.3, 125.6, 125.4. HRMS (EI): Calcd [M^+]: 177.0484. $[C_9H_9N_2S]^+$ Found: 177.0474.

2-((2-fluorophenyl)thio)-1*H*-imidazole (2ab) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-fluoroiodobenzene (0.087 mL, 0.75 mmol), 69 mg (71% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 123-125 ºC. R_f = 0.38 (50% hexane/EtOAc). ν_{max} = 3091, 3004, 2747, 2547, 1865, 1547, 1473, 1329, 1229, 1101, 1028 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.84 (bs, 1H, NH), 7.30-7.23-7.11 (m, 5H, Ph, CHCH), 6.90 (td, J = 8.3 Hz, 1.5 Hz, 1H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5 (d, *J* = 242.3 Hz), 132.8, 129.7 (d, *J* = 2.2 Hz), 128.7 (d, *J* = 7.6 Hz), 125.3 (d, *J* = 3.0 Hz), 122.6 (d, *J* = 17.5 Hz), 115.8, 115.6. HRMS (EI): Calcd [M^+]: 195.0390. $[C_9H_8N_2SF]^+$ Found: 195.0378.

2-((2-chlorophenyl)thio)-1*H*-imidazole (2ac) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-chloroiodobenzene (0.091 mL, 0.75 mmol), 80 mg (76% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 139-141 ºC. R_f = 0.36 (50% hexane/EtOAc). ν_{max} = 3098, 2902, 2771, 2640, 2548, 1755, 1454, 1327, 1255, 1100, 1030 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.97 (bs, 1H, NH), 7.48-7.18 (m, 5H, Ph, CHCH), 6.58 (d, *J* = 9.1 Hz, 1H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 136.0, 132.3, 129.6, 129.2, 128.0, 127.3, 127.0. HRMS (EI): Calcd [M^+]: 211.0094. $[C_9H_8N_2SCl]^+$ Found: 211.0090.

2-(*o*-tolylthio)-1*H*-imidazole (2ad) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-iodotoluene (0.096 mL, 0.75 mmol), 78 mg (82% yield) of the coupled product was obtained as an pale brown solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 115-116 ºC. R_f = 0.42 (50% hexane/EtOAc). ν_{max} = 3134, 3015, 2895, 2628, 2554, 1915, 1545, 1454, 1426, 1329, 1253, 1104, 1041 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.72 (bs, 1H, NH), 7.23-7.20 (m, 3H, Ph), 7.14-7.07 (m, 2H, CHCH), 6.78-6.75 (m, 1H, Ph), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.90, 135.5, 135.1, 134.4, 130.3, 127.7, 126.7, 126.4, 19.6. HRMS (EI): Calcd [M^+]: 191.0641. $[C_{10}H_{11}N_2S]^+$ Found: 190.0646.

2-((2,6-dimethylphenyl)thio)-1*H*-imidazole (2ae) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-iodo-1,3-dimethylbenzene (0.108 mL, 0.75 mmol), 61 mg (60% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 192-194 ºC. R_f = 0.54 (50% hexane/EtOAc). ν_{max} = 3434, 3146, 3025, 2692, 2641, 1931, 1661, 1556, 1460, 1331, 1254, 1093 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.13 (bs, 1H, NH), 7.21-6.85 (m, 5H, Ph, CHCH), 2.41 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.0, 142.2, 137.9, 130.5, 128.9, 128.3, 21.7. HRMS (EI): Calcd [M^+]: 205.0797. $[C_{11}H_{14}N_2S]^+$ Found: 205.0796.

2-((3-fluorophenyl)thio)-1*H*-imidazole (2af) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-fluoroiodobenzene (0.088 mL, 0.75 mmol), 78 mg (80% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 71-73 ºC. R_f = 0.38 (50% hexane/EtOAc). ν_{max} = 3068, 2996, 2752, 2630, 1862, 1599, 1473, 1416, 1327, 1263, 1097, 1062 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.89 (bs, 1H, NH), 7.38-7.20 (m, 3H, Ph, CHCH), 7.04 (td, *J* = 8.6 Hz, 2.5 Hz, 1H, Ph), 6.91 (t, *J* = 8.5 Hz, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 163.5, 161.1, 136.2 (d, *J* = 133.4 Hz), 131.1 (d, *J* = 8.4 Hz), 122.8 (d, *J* = 3.0 Hz), 113.4 (d, *J* = 23.6 Hz), 113.1 (d, *J* = 21.3 Hz). HRMS (EI): Calcd [M^+]: 195.0390. $[C_9H_8N_2SF]^+$ Found: 195.0387.

2-((3-chlorophenyl)thio)-1*H*-imidazole (2ag) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-chloroiodobenzene (0.093 mL, 0.75 mmol), 84 mg (80% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 120-122 ºC. R_f = 0.37 (50% hexane/EtOAc). ν_{max} = 3055, 2991, 2882, 2737, 2575, 1860, 1619, 1565, 1460, 1327, 1164, 1099, 1070 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.90 (bs, 1H, NH), 7.36-7.26 (m, 4H, Ph, CHCH), 7.10-7.07 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.5, 135.2, 133.8, 133.4, 130.9, 126.2, 126.1, 125.5. HRMS (EI): Calcd [M^+]: 211.0094. $[C_9H_8N_2SCl]^+$ Found: 211.0090.

2-((3-bromophenyl)thio)-1*H*-imidazole (2ah) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-bromoiodobenzene (0.096 mL, 0.75 mmol), 102 mg (80% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 129-131 ºC. R_f = 0.45 (50% hexane/EtOAc). ν_{max} = 3129, 3049, 2989, 2737, 2619, 1864, 1619, 1560, 1458, 1327, 1164, 1100, 1065 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.89 (bs, 1H, NH), 7.41 (d, *J* = 7.6 Hz, 2H, Ph), 7.29-7.24 (m, 2H, CHCH), 7.12 (d, *J* = 8.1 Hz, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 138.7, 133.4, 131.2, 129.1, 128.9, 125.5, 122.2. HRMS (EI): Calcd [M^+]: 254.9589. $[C_9H_8N_2SBr]^+$ Found: 254.9588.

2-((3-(trifluoromethyl)phenyl)thio)-1*H*-imidazole (2ai) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-iodobenzotrifluoride (0.108 mL, 0.75 mmol), 100 mg (82% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 136-137 ºC. R_f = 0.36 (50% hexane/EtOAc). ν_{max} = 3141, 3003, 2772, 2630, 1870, 1555, 1478, 1424, 1322, 1273, 1168, 1102, 1072 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.93 (bs, 1H, NH), 7.58-7.53 (m, 2H, CHCH), 7.40 (s, 2H, Ph), 7.29 (s, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 138.0, 130.8, 130.3, 130.1, 129.8, 125.1, 123.0 (qn, *J* = 4.5 Hz), 122.3. HRMS (EI): Calcd [M^+]: 245.0358. $[C_{10}H_8N_2SF_3]^+$ Found: 245.0360.

2-((3-methoxyphenyl)thio)-1*H*-imidazole (2aj) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-iodoanisole (0.089 mL, 0.75 mmol), 83 mg (81% yield) of the coupled product was obtained as an off white solid after purification by flash chromatography (hexane/ethyl acetate, 50:50). m.p. 109-110 ºC. R_f = 0.38 (50% hexane/EtOAc). ν_{max} = 3135, 2960, 2892, 2829, 2734, 2488, 1866, 1589, 1483, 1419, 1327, 1247, 1105, 1029 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.8 (bs, 1H, NH), 7.24-7.20 (m, 3H, Ph), 6.80-6.77 (m, 1H, Ph), 6.67-6.65 (m, 2H, CHCH), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 159.7, 137.2, 134.3, 130.2, 119.2, 112.7, 111.8, 55.1. HRMS (EI): Calcd [M^+]: 207.0590. $[C_{10}H_{11}N_2SO]^+$ Found: 207.0588.

1-(3-((1*H*-imidazol-2-yl)thio)phenyl)ethanone (2ak) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3`-iodoacetophenone (0.136 mL, 0.75 mmol), 92 mg (84% yield) of the coupled product was obtained as an brown solid after purification by flash chromatography (hexane/ethyl acetate, 40:60). m.p. 113-115 ºC. R_f = 0.35 (50% hexane/EtOAc). ν_{max} = 3359, 3135, 3062, 2998, 2576, 2521, 1864, 1690, 1563, 1422, 1249, 1160, 1100 cm^{-1}. ^1H NMR (400

MHz, DMSO-d_6): δ = 12.90 (bs, 1H, NH), 7.80 (d, *J* = 7.6 Hz, 1H, Ph), 7.67 (s, 1H, Ph), 7.47 (t, *J* = 7.6 Hz, 1H, Ph), 7.36 (d, *J* = 8.1 Hz, 1H, Ph), 7.27 (s, 2H, CHCH), 2.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 197.3, 137.6, 136.9, 131.6, 129.0, 129.7, 126.4, 126.3, 125.9, 26.7. HRMS (EI): Calcd [M^+]: 219.0590. $[C_{11}H_{11}N_2SO]^+$ Found: 219.0592.

2-(*m*-tolylthio)-1*H*-imidazole (2al) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-iodotoluene (0.102 mL, 0.75 mmol), 77 mg (81% yield) of the coupled product was obtained as an pale yellow solid after purification by flash chromatography (hexane/ethyl acetate, 50:50). m.p. 105-107 ºC. R_f = 0.48 (50% hexane/EtOAc). ν_{max} = 2996, 2889, 2744, 2581, 1866, 1591, 1474, 1421, 1330, 1101, 1080 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.75 (bs, 1H, NH), 7.22-7.17 (m, 3H, Ph), 7.02 (d, *J* = 8.1 Hz, 1H, CHCH), 6.96 (s, 1H, Ph), 6.90 (d, *J* = 7.1 Hz, 1H, CHCH), 2.23 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 139.5, 137.6, 136.4, 135.5, 130.0, 128.7, 128.0, 125.4, 21.8. HRMS (EI): Calcd [M^+]: 191.0641. $[C_{10}H_{11}N_2S]^+$ Found: 191.0640.

2-((3,5-dimethylphenyl)thio)-1*H*-imidazole (2am) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (0.108 mL, 0.75 mmol), 82 mg (80 % yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 171-173 ºC. R_f = 0.48 (50% hexane/EtOAc). ν_{max} = 3109, 3001, 2912, 2488, 1866, 1599, 1580, 1449, 1419, 1328, 1167, 1099, 1038 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.70 (bs, 1H, NH), 7.20 (s, 2H, CHCH), 6.84 (s, 1H, Ph), 6.75 (s, 2H, Ph), 2.19 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.118, 138.4, 135.2, 134.8, 128.1, 125.1, 20.8. HRMS (EI): Calcd [M^+]: 205.0797. $[C_{11}H_{14}N_2S]^+$ Found: 205.0799.

2-((4-fluorophenyl)thio)-1*H*-imidazole (2an) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-fluoroiodobenzene (0.087 mL, 0.75 mmol), 81 mg (83% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 55:45). m.p. 133-134 ºC. R_f = 0.40 (50% hexane/EtOAc). ν_{max} = 3146, 3094, 2629, 2544, 1856, 1587, 1489, 1418, 1326, 1220, 1103 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.75 (bs, 1H, NH), 7.26-7.16 (m, 6H, Ph, CHCH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 162.3, 147.5 (d, *J* = 24.2 Hz), 130.8 (d, *J* = 4.0 Hz), 123.3 (d, *J* = 21.3 Hz), 123.3 (d, *J* = 24.2 Hz). HRMS (EI): Calcd [M^+]: 195.0390. $[C_9H_8N_2SF]^+$ Found: 195.0391.

2-((4-chlorophenyl)thio)-1*H*-imidazole (2ao) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-chloroiodobenzene (0.179 g, 0.75 mmol), 93 mg (89% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 139-141 ºC. R_f = 0.41 (50% hexane/EtOAc). ν_{max} = 3097, 2994, 2880, 2817, 2756, 2629, 1831, 1620, 1546, 1476, 1416, 1325, 1089 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.81 (bs, 1H, NH), 7.39-7.37 (m, 2H, Ph), 7.24 (s, 2H, Ph), 7.14-7.12 (m, 2H, CHCH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 134.9, 134.1, 131.1, 129.2, 129.1, 48.6. HRMS (EI): Calcd [M^+]: 211.0094. $[C_9H_8N_2SCl]^+$ Found: 211.0094.

2-((4-bromophenyl)thio)-1*H*-imidazole (2ap) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-bromoiodobenzene (0.212 g, 0.75 mmol), 107 mg (84% yield) of the coupled product was obtained as an brown-yellow solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 169-171 ºC. R_f = 0.41 (50% hexane/EtOAc). ν_{max} = 2996, 2824, 2487, 1864, 1611, 1472, 1418, 1328, 1103, 1085, 1006 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.83 (bs, 1H, NH), 7.50 (d, *J* = 8.6 Hz, 2H, Ph), 7.24 (s, 2H, CHCH), 7.06 (d, *J* = 8.6 Hz, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 202.0, 135.5, 133.9, 132.1, 129.1, 119.3. HRMS (EI): Calcd [M^+]: 254.9589. $[C_9H_8N_2SBr]^+$ Found: 254.9590.

2-((4-(trifluoromethyl)phenyl)thio)-1*H*-imidazole (2aq) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-iodobenzotrifluoride (0.110 mL, 0.75 mmol), 100 mg (82% yield) of the coupled product was obtained as an off white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 145-147 ºC. R_f = 0.36 (50% hexane/EtOAc). ν_{max} = 3097, 2997, 2889, 2821, 2633, 2548, 1869, 1607, 1420, 1404, 1330, 1161, 1087, 1012 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.92 (bs, 1H, NH), 7.66 (d, *J* = 8.6 Hz, 2H, Ph), 7.31 (s, 2H, CHCH), 7.24 (d, *J* = 8.6 Hz, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.3, 132.8, 126.6, 126.3, 126.0 (qn, *J* = 3.8 Hz), 125.5, 122.8. HRMS (EI): Calcd [M^+]: 245.0358. $[C_{10}H_8N_2SF_3]^+$ Found: 245.0359.

2-((4-methoxyphenyl)thio)-1*H*-imidazole (2ar) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-iodoanisole (0.176 g, 0.75 mmol), 83 mg (81% yield) of the coupled product was obtained as a grey solid after purification by flash chromatography (hexane/ethyl acetate, 50:50). m.p. 153-155 ºC. R_f = 0.42 (50% hexane/EtOAc). ν_{max} = 3067, 3003, 2886, 2735, 2621, 1865, 1645, 1596, 1495, 1326, 1255, 1170, 1094, 1023 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.60 (bs, 1H, NH), 7.24 (d, *J* = 8.6 Hz, 2H, Ph), 7.14 (s, 2H, CHCH), 6.91 (d, *J* = 8.6 Hz, 2H, Ph), 3.72 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.6, 159.6, 136.6, 132.1, 125.8, 115.8, 55.3. HRMS (EI): Calcd [M^+]: 207.0590. $[C_{10}H_{11}N_2SO]^+$ Found: 207.0588.

1-(4-((1*H*-imidazol-2-yl)thio)phenyl)ethanone (2as) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4`-iodoacetophenone (0.185 g, 0.75 mmol), 96 mg (88% yield) of the coupled product was obtained as a brown solid after purification by flash chromatography (hexane/ethyl acetate, 40:60). m.p. 120-122 ºC. R_f = 0.38 (50% hexane/EtOAc). ν_{max} = 3103, 3003, 2770, 2642, 1873, 1676, 1590, 1333, 1264, 1106, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.96 (bs, 1H, NH), 7.87 (d, *J* = 8.0 Hz, 2H, Ph), 7.31 (s, 2H, CHCH), 7.14 (d, *J* = 8.0 Hz, 2H, Ph), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.9, 143.1, 137.6, 134.4, 132.8, 129.0, 125.9, 26.6. HRMS (EI): Calcd [M^+]: 219.0590. $[C_{11}H_{11}N_2SO]^+$ Found: 219.0593.

2-(*p*-tolylthio)-1*H*-imidazole (2at) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 4-iodotoluene (0.164 g, 0.75 mmol), 81 mg (85% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 50:50). m.p. 129-131 ºC. R_f = 0.48 (50% hexane/EtOAc). ν_{max} = 3145, 3096, 2993, 2746, 2630, 1849, 1547, 1492, 1416, 1326, 1103, 1096, 1017 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (bs, 1H, NH), 7.18 (s, 2H, CHCH), 7.13 (d, *J* = 8.1 Hz, 2H, Ph), 7.07 (d, *J* = 8.6, 2H, Ph), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.1, 135.3, 131.9, 129.8, 128.0, 126.7, 20.5. HRMS (EI): Calcd [M^+]: 191.0641. $[C_{10}H_{11}N_2S]^+$ Found: 191.0644.

2-(naphthalen-1-ylthio)-1*H*-imidazole (2au) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 1-iodonaphthalene (0.110 mL, 0.75 mmol), 79 mg (70% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 191-193 ºC. R_f = 0.62 (50% hexane/EtOAc).

ν_{max} = 2994, 2539, 1866, 1619, 1551, 1419, 1329, 1255, 1100, 1064 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.75 (bs, 1H, NH), 8.31 (d, *J* = 7.6 Hz, 1H，Ph), 7.97 (d, *J* = 8.1 Hz, 1H，Ph), 7.86 (d, *J* = 8.6 Hz, 1H，Ph), 7.65-7.57 (m, 2H，CHCH), 7.64 (t, *J* = 8.1 Hz, 1H，Ph), 7.25-7.21 (m, 3H，Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 135.2, 134.7, 133.5, 132.1, 131.0, 128.6, 127.6, 127.5, 126.9, 126.5, 125.9, 124.0. HRMS (EI): Calcd $[M^+]$: 227.0641. $[C_{13}H_{11}N_2S]^+$ Found: 227.0640.

2-(naphthalen-2-ylthio)-1*H*-imidazole (2av) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-fluoroiodobenzene (0.191 g, 0.75 mmol), 90 mg (80% yield) of the coupled product was obtained as an off white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 152-154 ºC. R_f = 0.62 (50% hexane/EtOAc). ν_{max} = 3055, 2629, 1859, 1621, 1499, 1416, 1325, 1268, 1131, 1102, 1017 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.83 (bs, 1H，NH), 7.87 (d, *J* = 8.6 Hz, 2H，Ph), 7.78 (d, *J* = 8.6 Hz, 1H，Ph), 7.96 (s, 1H，Ph), 7.52-7.46 (m, 2H，CHCH), 7.26-7.23 (m, 3H，Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.4, 134.7, 133.2, 133.1, 131.4, 130.4, 128.8, 127.7, 127.0, 126.9, 126.1, 125.6. HRMS (EI): Calcd $[M^+]$: 227.0641. $[C_{13}H_{11}N_2S]^+$ Found: 227.0638.

2-(phenylthio)-1*H*-imidazole (2aa) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and bromobenzene (0.079 mL, 0.75 mmol), 18 mg (20% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 102-104 ºC. R_f = 0.46 (50% hexane/EtOAc). ν_{max} = 3047, 3001, 2700, 2542, 1860, 1550, 1310, 1211, 1087, 1020 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.74 (bs, 1H, NH), 7.31 (t, *J* = 7.6 Hz, 2H, Ph), 7.23-7.18 (m, 3H, Ph), 7.12 (d, *J* = 8.1 Hz, 2H, CHCH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 135.9, 134.5, 129.3, 127.3, 125.6, 125.4. HRMS (EI): Calcd $[M^+]$: 177.0484. $[C_9H_9N_2S]^+$ Found: 177.0474.

2-(thiophen-2-ylthio)-1*H*-imidazole (3aa) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-iodothiophene (0.083 mL, 0.75 mmol), 55 mg (60% yield) of the coupled product was obtained as a yellow solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 148-150 ºC. R_f = 0.36 (50% hexane/EtOAc). ν_{max} = 3085, 2993, 2812, 2744, 2621, 1804, 1542, 1415, 1323, 1216, 1096 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.61 (bs, 1H, NH), 7.64 (dd, *J* = 6.7 Hz, 1.0 Hz, 1H, CHCH), 7.28 (dd, *J* = 6.7 Hz, 1.0 Hz, 1H, CHCH), 7.10-7.03 (m, 3H, heteroaryl). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.9, 135.6, 133.4, 130.8, 127.9, 125.1. HRMS (EI): Calcd $[M^+]$: 183.0048. $[C_7H_7N_2S_2]^+$ Found: 183.0050.

2-(thiophen-3-ylthio)-1*H*-imidazole (3ab) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-iodothiophene (0.076 mL, 0.75 mmol), 77 mg (85% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 145-147 ºC. R_f = 0.35 (50% hexane/EtOAc). ν_{max} = 3105, 2993, 2884, 2816, 2741, 2621, 1860, 1614, 1547, 1419, 1326, 1195, 1098 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.54 (bs, 1H, NH), 7.60-7.58 (m, 1H, heteroaryl), 7.44-7.43 (m, 1H，heteroaryl), 7.14 (s, 2H，CHCH), 6.98 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H，heteroaryl). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.2, 129.9, 129.8, 128.4, 125.8, 125.3. HRMS (EI): Calcd $[M^+]$: 183.0048. $[C_7H_7N_2S_2]^+$ Found: 183.0050.

1-(5-((1*H*-imidazol-2-yl)thio)thiophen-2-yl)ethanone (3ac) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-acetyl-5-iodothiophene (0.189 g, 0.75 mmol), 69 mg (62% yield) of the coupled product was obtained as an brownish-yellow solid after purification by flash chromatography (hexane/ethyl acetate, 30:70). m.p. 144-146 ºC. R_f = 0.34 (50% hexane/EtOAc). ν_{max} = 3146, 3090, 2920, 1654, 1520, 1413, 1273, 1120, 1104, 1014 cm^{-1}. ^1H NMR (400 MHz, DMSO-d): δ = 12.89 (bs, 1H，NH), 7.79 (d, *J* = 4.0 Hz, 1H，heteroaryl), 7.22-7.19 (m, 3H, heteroaryl, CHCH), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d): δ = 206.3, 190.0, 149.8, 144.9, 143.9, 134.2, 130.2, 26.3. HRMS (EI): Calcd $[M^+]$: 225.0154. $[C_9H_9N_2S_2O]^+$ Found: 225.0155.

2-(benzo[*b*]thiophen-2-ylthio)-1*H*-imidazole (3ad) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-iodobenzothiophene (0.195 mL, 0.75 mmol), 81 mg (70% yield) of the coupled product was obtained as an yellowish solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 186-188 ºC. R_f = 0.46 (50% hexane/EtOAc). ν_{max} = 3433, 2992, 2579, 1861, 1618, 1497, 1419, 1326, 1245, 1127, 1101 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.84 (bs, 1H, NH), 7.87 (d, *J* = 7.6 Hz, 1H, heteroaryl), 7.79 (d, *J* = 7.6 Hz, 1H, heteroaryl), 7.53 (s, 1H, heteroaryl), 7.38-7.31 (m, 2H, CHCH), 7.18 (s, 2H, heteroaryl). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 140.7, 139.3, 134.4, 128.6, 128.1, 127.2, 124.7, 123.4, 122.1. HRMS (EI): Calcd $[M^+]$: 233.0205. $[C_{11}H_9N_2S_2]^+$ Found: 233.0205.

2-(thiophen-2-ylthio)-1*H*-imidazole (3aa) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 2-bromothiophene (0.073 mL, 0.75 mmol), 14 mg (15% yield) of the coupled product was obtained as a yellow solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 148-150 ºC. R_f = 0.36 (50% hexane/EtOAc). ν_{max} = 3085, 2993, 2812, 2744, 2621, 1804, 1542, 1415, 1323, 1216, 1096 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.61 (bs, 1H, NH), 7.64 (dd, *J* = 6.7 Hz, 1.0 Hz, 1H, CHCH), 7.28 (dd, *J* = 6.7 Hz, 1.0 Hz, 1H, CHCH), 7.10-7.03 (m, 3H, heteroaryl). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.9, 135.6, 133.4, 130.8, 127.9, 125.1. HRMS (EI): Calcd $[M^+]$: 183.0048. $[C_7H_7N_2S_2]^+$ Found: 183.0050.

2-(thiophen-3-ylthio)-1*H*-imidazole (3ab) Following the general procedure using 2-mercaptoimidazole (0.501 g, 0.50 mmol) and 3-bromothiophene (0.070 mL, 0.75 mmol), 16 mg (17% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 60:40). m.p. 145-147 ºC. R_f = 0.35 (50% hexane/EtOAc). ν_{max} = 3105, 2993, 2884, 2816, 2741, 2621, 1860, 1614, 1547, 1419, 1326, 1195, 1098 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.54 (bs, 1H, NH), 7.60-7.58 (m, 1H, heteroaryl), 7.44-7.43 (m, 1H，heteroaryl), 7.14 (s, 2H，CHCH), 6.98 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H，heteroaryl). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.2, 129.9, 129.8, 128.4, 125.8, 125.3. HRMS (EI): Calcd $[M^+]$: 183.0048. $[C_7H_7N_2S_2]^+$ Found: 183.0050.

1-methyl-2-(phenylthio)-1*H*-imidazole (4aa)[34] Following the general procedure using 2-mercapto-1-methylimidazole (0.057 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 69 mg (73% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 80:20). m.p. 94-96 ºC. R_f = 0.34 (50% hexane/EtOAc). ν_{max} = 3040, 3003, 2715, 2541, 1863, 1554, 1311, 1230, 1089, 1021 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.46 (s, 1H, Ph), 7.31 (t, *J* = 7.1 Hz, 2H, Ph), 7.21 (t, *J* = 8.1 Hz, 1H, Ph), 7.11 (s, 1H, Ph), 7.06 (d, *J* = 7.6 Hz, 2H, CHCH), 3.61 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.0, 135.0, 129.6, 129.4, 127.0, 126.4, 125.0, 33.4. HRMS (EI): Calcd $[M^+]$: 191.0641. $[C_{10}H_{11}N_2S]^+$ Found: 191.0642.

4-methyl-3-(phenylthio)-4*H*-1,2,4-triazole (4ba) Following the general procedure using 4-methyl-4H-1,2,4-triazole-3-thiol (0.058 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 91 mg (95% yield) of the coupled product was obtained as a yellow solid after purification by flash chromatography (dichloromethane/methanol, 95:5). m.p. 71-73 ºC. R_f = 0.54 (50% hexane/EtOAc). ν_{max} = 3410 bs, 3096, 2995, 1958, 1751, 1645, 1582, 1505, 1481, 1330, 1205, 1082, 1018 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.73 (s, 1H, C<u>H</u>), 7.37 (t, *J* = 6.6 Hz, 2H, Ph), 7.31-7.28 (m, 1H, Ph), 7.25-7.23 (m, 2H, Ph), 3.57 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 147.4, 132.0, 129.7, 128.6, 127.5, 31.31. HRMS (EI): Calcd [M^+]: 192.0593. [$C_9H_{10}N_3S$]$^+$ Found: 192.0594.

3-(phenylthio)-1*H*-1,2,4-triazole (4ca) Following the general procedure using 1*H*-1,2,4-triazole-3-thiol (0.051 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 35 mg (40% yield) of the coupled product was obtained as a yellow oil after purification by flash chromatography (hexane/ethyl acetate, 65:35). R_f = 0.26 (50% hexane/EtOAc). ν_{max} = 3055, 2992, 1970, 1655, 1643, 1588, 1500, 1400, 1332, 1247, 1082, 1018 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 14.34 (bs, 1H, N<u>H</u>), 8.66 (s, 1H, C<u>H</u>), 7.37-7.28 (m, 5H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.4, 142.2, 132.9, 129.9, 129.1, 127.2. HRMS (EI): Calcd [M^+]: 178.0437. [$C_8H_8N_3S$]$^+$ Found: 178.0440.

1-methyl-5-(phenylthio)-1*H*-tetrazole (4da)[35] Following the general procedure using 5-mercapto-1-methyltetrazole (0.058 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 81 mg (84% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 85:15). m.p. 76-78 ºC. R_f = 0.51 (50% hexane/EtOAc). ν_{max} = 3010, 2992, 1766, 1752, 1642, 1555, 1500, 1400, 1321, 1208, 1018 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.53-7.51 (m, 2H, Ph), 7.45-7.43 (m, 3H, Ph), 4.01 (s, 3H, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.9, 131.8, 129.9, 129.1, 128.5, 34.2. HRMS (EI): Calcd [M^+]: 193.0546. [$C_8H_9N_4S$]$^+$ Found: 193.0544.

4-phenyl-2-(phenylthio)-1*H*-imidazole (4ea) Following the general procedure using 4-phenylimidazole-2-thiol (0.088 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 98 mg (78% yield) of the coupled product was obtained as a yellow solid after purification by flash chromatography (hexane/ethyl acetate, 85:15). m.p. 122-124 ºC. R_f = 0.51 (50% hexane/EtOAc). ν_{max} = 3066, 2996, 2766, 2441, 1866, 1652, 1555, 1522, 1341, 1210, 1201, 1033, 1014 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.98 (bs, 1H, N<u>H</u>), 7.80 (d, J = 7.6 Hz, 3H, Ph), 7.39-7.30 (m, 4H, Ph, C<u>H</u>), 7.24-7.21 (m, 4H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.5, 135.6, 135.5, 133.0, 129.3, 128.6, 127.4, 126.7, 126.5, 124.3, 54.9. HRMS (EI): Calcd [M^+]: 253.0797. [$C_{15}H_{13}N_2S$]$^+$ Found: 253.0799.

4,5-diphenyl-2-(phenylthio)-1*H*-imidazole (4fa)[33] Following the general procedure using 4,5-diphenyl-2-imidazolethiol (0.126 g, 0.50 mmol) and iodobenzene (0.084 mL, 0.75 mmol), 128 mg (78% yield) of the coupled product was obtained as an off-white solid after purification by flash chromatography (hexane/ethyl acetate, 85:15). m.p. 148-149 ºC. R_f = 0.63 (50% hexane/EtOAc). ν_{max} = 3055, 2978, 2762, 2400, 1861, 1612, 1542, 1501, 1304, 1214, 1043, 1007 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 13.15 (bs, 1H, N<u>H</u>), 7.48-7.25 (m, 15H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 135.5, 135.2, 129.4, 128.7, 128.3, 128.1, 127.9, 127.1, 126.8, 126.6. HRMS (EI): Calcd [M^+]: 329.1110. [$C_{21}H_{17}N_2S$]$^+$ Found: 329.1111.

Acknowledgments

We would like to thank the National Institute of Education and Nanyang Technological University (RP 5/13 TYC) for funding this work.

References and notes

1. Chimirri, A.; Grasso, S.; Molica, C.; Monforte, A.; Monforte, P.; Zappalà, M.; Bruno, G.; Nicolò, F.; Witvrouw, M.; Jonckeere, H. *Antivir. Chem. Chemoth.* **1997**, *8*, 363-370.
2. Buckheit, R. W.; Hollingshead, M. G.; Germany-Decker, J.; White, E. L.; McMahon, J. B.; Allen, L. B.; Ross, L. J.; Decker, W. D.; Westbrook, L.; Shannon, W. M. *Antivir. Res.* **1993**, *21*, 247-265.
3. De Palma, A. M.; Heggermont, W.; Lanke, K.; Coutard, B.; Bergmann, M.; Monforte, A.-M.; Canard, B.; De Clercq, E.; Chimirri, A.; Pürstinger, G. *J. Virol.* **2008**, *82*, 4720-4730.
4. Ferrini, P. G.; Goschke, R. *U.S. Patent No. 4632930*. **1984**.
5. Gilman, N. W.; Chen, W. Y. *U.S. Patent No. 4973599*, **1990**.
6. Carcanague, D.; Shue, Y.-K.; Wuonola, M. A.; Uria-Nickelsen, M.; Joubran, C.; Abedi, J. K.; Jones, J.; Kühler, T. C. *J. Med. Chem.* **2002**, *45*, 4300-4309.
7. de Assis, J. V.; Couri, M. R. C.; Porto, R. S.; de Almeida, W. B.; dos Santos, L. H. R.; Diniz, R.; de Almeida, M. V. *J. Heterocycl. Chem.* **2013**, *50*, E142-E147.
8. Bennamane, N.; Zaïoua, K.; Akacem, Y.; Kaoua, R.; Bentarzi, Y.; Bakhta, S.; Nedjar-Kolli, B.; Ouhab, L. *Org. Comm.* **2009**, *2*.
9. Jung, E. J.; Hur, M.; Kim, Y. L.; Lee, G. H.; Kim, J.; Kim, I.; Lee, M.; Han, H.-K.; Kim, M.-S.; Hwang, S. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 1005-1013.
10. Barrish, J. C.; Spergel, S. H.; *World Patent No. 1999009845*, **1999**.
11. Alvarez, C. S.; Baldwin, J. J.; Bishop, R. W.; Cooper, A. B.; Desai, J. A.; Doll, R. J.; Girijavallabhan, V. M.; Guzi, T.; Huang, C. Y.; James, R. A.; *World Patent No. 1998011092*, **2002**.
12. Vecchia, L. D.; Dellureficio, J.; Kisis, B.; Vlattas, I. *J. Heterocycl. Chem.* **1983**, *20*, 1287-1294.
13. Vlattas, I.; *U.S. Patent No. 4391808*, **1983**.
14. Schwab, R. S.; Singh, D.; Alberto, E. E.; Piquini, P.; Rodrigues, O. E.; Braga, A. L. *Catal. Sci. Tech.* **2011**, *1*, 569-573.
15. Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205-3220.
16. Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chemistry* **2010**, *16*, 2355-2359.
17. Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180-2181.
18. Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385-1389.
19. Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100-5105.
20. Feng, Y.; Wang, H.; Sun, F.; Li, Y.; Fu, X.; Jin, K. *Tetrahedron* **2009**, *65*, 9737-9741.
21. Herrero, M. T.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2009**, *65*, 1500-1503.
22. Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971-1976.
23. Li, Y.; Li, X.; Wang, H.; Chen, T.; Xie, Y. *Synthesis* **2010**, 3602-3608.
24. Xu, H.-J.; Zhao, X.-Y.; Deng, J.; Fu, Y.; Feng, Y.-S. *Tetrahedron Lett.* **2009**, *50*, 434-437.
25. Zhang, X.-Y.; Zhang, X.-Y.; Guo, S.-R. *J. of Sulfur Chem.* **2011**, *32*, 23 - 35.
26. Rao, H.; Fu, H. *Synlett* **2011**, 745-769.
27. Li, C.-J.; Trost, B. M. *Proc. Nat. Acad. Sci.* **2008**, *105*, 13197-13202.
28. Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606-9607.
29. Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484-1487.
30. Xu, X.-B.; Liu, J.; Zhang, J.-J.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550-553.
31. Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495-3498.

32. Sekar, R.; Srinivasan, M.; Marcelis, A. T.; Sambandam, A. *Tetrahedron Lett.* **2011**, *52*, 3347-3352.
33. Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880-2883.
34. Kao, H.-L.; Chen, C.-K.; Wang, Y.-J.; Lee, C.-F. *Eur. J. Org. Chem.* **2011**, *2011*, 1776-1781.
35. Niu, L.-F.; Cai, Y.; Liang, C.; Hui, X.-P.; Xu, P.-F. *Tetrahedron* **2011**, *67*, 2878-2881.
36. Zhu, H.-J.; Ren, Y.; Ren, J.; Chu, S.-Y. *J. Mol. Struct.* **2005**, *730*, 199-205.
37. Perez-Peña, J.; Gonzalez-Davila, M.; Suarez-Tangil, M.; Hernandez-Brito, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2045-2053.
38. Yong, F.-F.; Teo, Y.-C.; Chua, G.-L.; Lim, G. S.; Lin, Y. *Tetrahedron Lett.* **2011**, *52*, 1169-1172.
39. Yong, F.-F.; Teo, Y.-C. *Synlett* **2010**, 3068-3072.
40. Tan, B. Y.-H.; Teo, Y.-C.; Seow, A.-H. *Eur. J. Org. Chem.* **2013**, *7*, *1541-1546*
41. Yong, F.-F.; Teo, Y.-C.; Yan, Y.-K.; Chua, G.-L. *Synlett* **2012**, 101-106.
42. Tan, Y. H.; Teo, Y. C. *Org. Biomol. Chem.* **2014**, 12, 7478-7481
43. Tan, B. Y.-H.; Teo, Y.-C. *Synlett* **2015**, 1697-1701.
44. Yong, F.-F.; Teo, Y.-C.; Tay, S.-H.; Tan, B. Y.-H.; Lim, K.-H. *Tetrahedron Lett.* **2011**, *52*, 1161-1164.
45. Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613-5616.
46. Xu, H. J.; Zheng, F. Y.; Liang, Y. F.; Cai, Z. Y.; Feng, Y. S.; Che, D. Q. *Tetrahedron Lett.* **2010**, *51*, 669-671.
47. Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, 640-643.
48. Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295-7298.
49. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337-2364.
50. Sperotto, E.; van Klink, G. P.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338-10351.
51. Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971.
52. Zou, J.-F.; Huang, W.-S.; Li, L.; Xu, Z.; Zheng, Z.-J.; Yang, K.-F.; Xu, L.-W. *RSC Adv.* **2015**, *5*, 30389-30393.
53. Song, J. H.; Sailor, M. J. *Inorg. Chem.* **1998**, *37*, 3355-3360.
54. Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247-260.

Supplementary Material

NMR spectra of new compounds related to this article can be found at http://dx.doi.org/