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Efficient copper(I)-catalyzed C–S cross-coupling of thiols with aryl halides in an aqueous two-phase system

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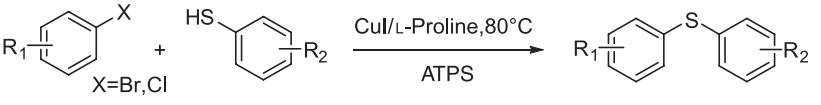
A mild and convenient C–S bond formation reaction catalyzed by CuI/L-proline in an aqueous two-phase system was achieved, providing a simple method for the synthesis of aryl sulfides in good yields.



Keywords: C–S cross-coupling reactions; CuI; thiols; aryl halides; aqueous two-phase system

1. Introduction

C(aryl)–S bonds are present in a large number of molecules that are of interest as pharmaceuticals and as useful polymeric materials. For this reason, the development of efficient S-arylation methods is a subject of interest in organic chemistry (*1–3*). Transition metal-catalyzed or -mediated arylation of thiols is a direct and powerful method to form these products. Although palladium-catalyzed C–S bond formation has achieved some good results (*4–7*), the use of copper catalysts for this transformation is still attractive from an industrial perspective (*8–10*). Traditional copper-mediated couplings between thiols and aryl halides have required the use of copper salts in greater than stoichiometric amounts, polar solvents such as HMPA, and high temperatures around 200 °C (*11*). Recently, along with the development of the research on mild copper-catalyzed aromatic carbon–heteroatom bond formations, copper-catalyzed C–S bond formation has received attention and this approach is still attractive owing to the advantages of copper over other metals, such as its price and minor toxicity than Pd and Ni (*12*, *13*).

The use of water as a solvent for organic reactions has been extensive in recent years (*14–18*) since water is cheap, nontoxic, safe, and environmentally benign relative to organic solvents. Recently, Rout *et al*. (*19*) described a procedure for C–S bond formation by using a combination

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of CuI and tetrabutyl ammonium bromide (TBAB) in water, but the reaction time is too long. Considering the lack of effective methods to synthesize aryl thioethers and their considerable interest, our group developed a new efficient protocol for the CuI-catalyzed S-arylation of aryl thiols with aryl bromides and chlorides in an aqueous two-phase system (ATPS).

ATPSs were mainly composed of two-incompatible polymers (e.g. dextran/poly ethylene glycol/water) or an organic solvent and a salt (e.g. ethanol/phosphate/water), and it was widely used in biochemistry (*20*). Our recent results on C–C bond formation in an ATPS encouraged us to extend the system for C–S bond formation (*21, 22*); thus, in continuation of our work on coupling reactions, herein, we report a general, efficient protocol for copper-catalyzed C–S coupling in an ATPS.

2. Results and discussion

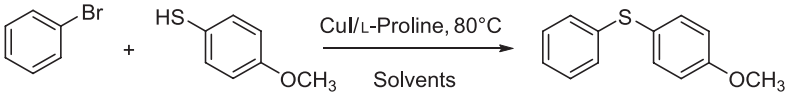
Our experiments were first conducted by coupling 4-methoxyl thiophenol with bromobenzene catalyzed by 5 mol% of copper (I) iodide and 10 mol% of L-proline, which was proved to be an effective catalyst system in many researches in various solvents (*23–25*). As indicated in Table 1, in pure water, only 62% conversion was obtained after 6 h (Table 1, Entries 2 and 4). Addition of PTC (e.g. TBAB) led to a gradual increase in the conversion rate (Table 1, Entries 1 and 3). In anhydrous ethanol, only 78% conversion was achieved after 6 h (Table 1, Entries 5–8); we also scanned other traditional solvents; polar solvents were better than less polar solvents (Table 1, Entries 9–12). We then scanned the various ATPS solvents. We selected three kinds of typical ATPS as reaction solvents to find out the best one for the cross-coupling reaction; to our surprise, the cross-coupling reaction (Table 1, Entry 16) proceeded to give 98% yield catalyzed with CuI/L-proline in EtOH/K_3PO_4/water (add the inorganic salt to the mixture of 6 ml of water and 4 ml

Table 1. The effects of different solvents in the coupling of 4-methoxyl thiophenol with bromobenzene catalyzed by CuI/L-proline.[a]

Entry	Solvent	Inorganic salts	Catalyst	Yield[b] (%)
1	Water	K_2CO_3	CuI (add PTC)	45 (52)
2	Water	K_2CO_3	CuI/L-proline	52
3	Water	K_3PO_4	CuI (add PTC)	57 (59)
4	Water	K_3PO_4	CuI/L-proline	62
5	EtOH	K_2CO_3	CuI (or CuO)	73 (62)
6	EtOH	K_2CO_3	CuI/L-proline	74
7	EtOH	K_3PO_4	CuI (or $Cu(OAc)_2$)	71 (66)
8	EtOH	K_3PO_4	CuI/L-proline	78
9	DMF	K_3PO_4	CuI/L-proline	82
10	DMSO	K_3PO_4	CuI/L-proline	80
11	1,4-dioxane	K_3PO_4	CuI/ L-proline	73
12	Toluene	K_3PO_4	CuI/L-proline	69
13	EtOH/water	K_2CO_3	CuI	83
14	EtOH/water	K_2CO_3	CuI/L-proline	93
15	EtOH/water	K_3PO_4	CuI (or CuO)	88 (72)
16	EtOH/water	K_3PO_4	CuI/L-proline	98
17	EtOH/water	K_2HPO_4	CuI/L-proline	91
18	Acetone/water	K_2CO_3	CuI/L-proline	82
19	Acetone/water	K_3PO_4	CuI/L-proline	85
20	PEG2000/water	K_2CO_3	CuI/L-proline	86
21	PEG2000/water	K_3PO_4	CuI/L-proline	89
22	EtOH/water	K_3PO_4	$Cu(OAc)_2$)/L-proline	78
23	EtOH/water	K_3PO_4	CuO/L-proline	82

Notes: [a]Reaction conditions: 4-methoxyl thiophenol (5.5 mmol), bromobenzene (5 mmol), 5 mol% of CuI, 10 mol% of L-proline, 12 mmol base, in 10 ml of solvent at 80 °C for 6 h in air atmosphere.
[b]Isolated yield (average of two runs).

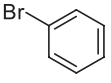
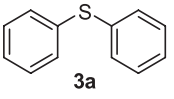
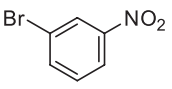
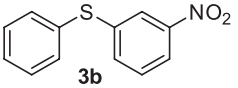
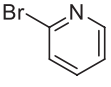
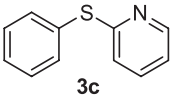
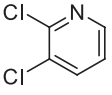
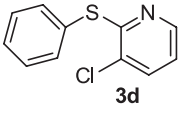
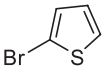
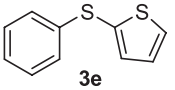
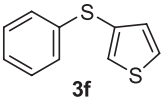
of EtOH, then the mixture solution separates into two phases clearly) in an ATPS refluxed for 6 h, the acetone/K_3PO_4 system (add the inorganic salt to the mixture of 6 ml of water and 4 ml of acetone, then the mixture solution separates into two phases clearly) proceeded to give 85% yield (Table 1, Entries 18 and 19), and the PEG2000/K_2HPO_4 system gave 89% yield (add the inorganic salt to the mixture of 6 ml of water and 4 g of PEG2000, then the mixture solution separates into two phases clearly; Table 1, Entries 20 and 21), while there was no reaction in the acid ATPS such as acetone/$(NH_4)_2SO_4$ or PEG2000/$(NH_4)_2SO_4$ system and a mediate yield was obtained in the ATPS catalyzed only by the CuI without an amino acid. Lastly, using the Cu(II) salts such as $Cu(OAc)_2$ and CuO as catalysts to promote the coupling reaction, the corresponding diaryl sulfide was obtained in 62–82% yield (Table 1, Entries 5, 7, 15, 22, and 23). From all those experimental data in Table 1, we consider that the ATPS with the catalyst system CuI/L-proline is better than pure water, ethanol, DMF and other traditional solvents for the cross-coupling reaction and that the optimal condition for the cross-coupling reaction is the EtOH/K_3PO_4 ATPS as a solvent catalyzed by CuI/L-proline (Scheme 1).



Scheme 1. Optimization of the reaction conditions.

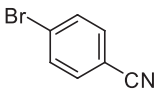
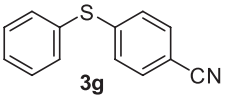
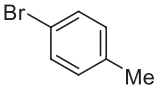
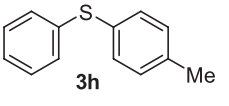
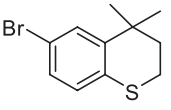
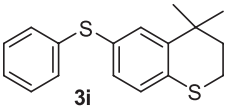
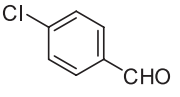
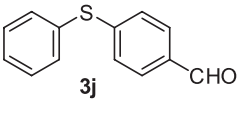
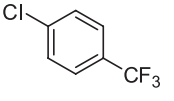
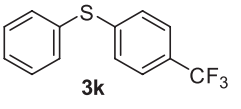
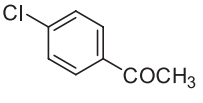
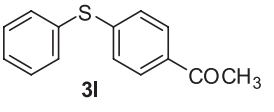
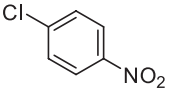
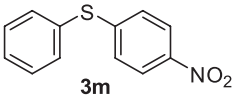
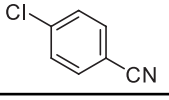
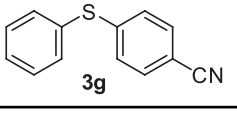
To explore the scope of the present reaction and expand the scope of our solvent system, we examined different aryl halides (Table 2). All the aryl halides reacted with thiophenol to give the

Table 2. Cross-coupling of thiophenol with aryl halides in the EtOH/K_3PO_4/water ATPS.[a]

Entry	Halides	Aryl sulfides	Time (h)	Yield (%)[b]
1		 **3a**	6	98
2		 **3b**	4	97
3		 **3c**	5	95
4		 **3d**	8	84
5		 **3e**	8	83
6		 **3f**	6	85

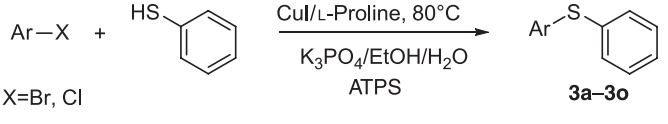
(*Continued*)

Table 2. *Continued*.

Entry	Halides	Aryl sulfides	Time (h)	Yield (%)[b]
7		 **3g**	5	95
8		 **3h**	6	96
9		 **3i**	6	97
10		 **3j**	7	95
11		 **3k**	6	92
12		 **3l**	4	97
13		 **3m**	5	98
14		 **3g**	6	94

Notes: [a]Reaction conditions: thiophenol (5.5 mmol), halides (5 mmol), 5 mol% of CuI, 10 mol% of L-proline, 12 mmol of K_3PO_4, 6 ml of water, and 4 mL of EtOH refluxed at 80 °C for 6 h. [b]Isolated yield (average of two runs).

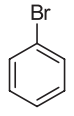
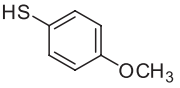
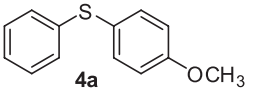
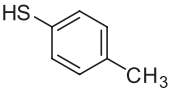
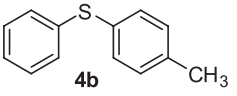
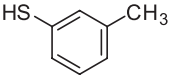
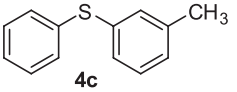
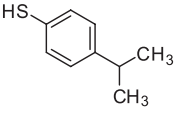
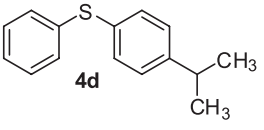
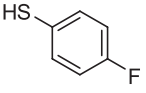
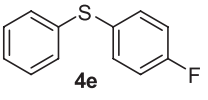
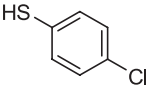
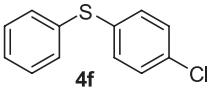
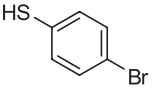
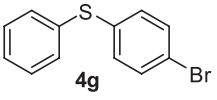
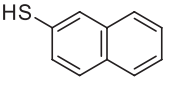
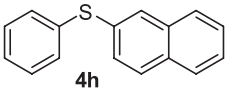
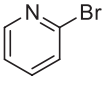
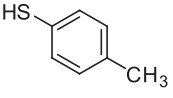
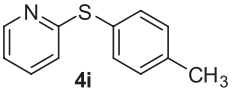
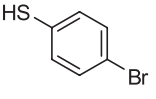
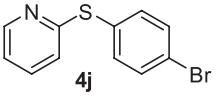
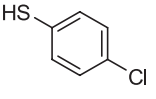
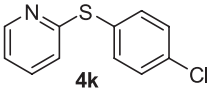
corresponding aryl sulfides in good yields for 4–8 h in the presence of 5 mol% of CuI and 10 mol% of L-proline using the EtOH/K_3PO_4/water ATPS as the reaction solvent (Table 2, Entries 1–14) (Scheme 2).



Scheme 2. C–S Coupling of various halides with thiophenol.

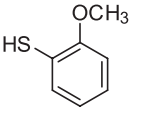
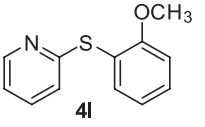
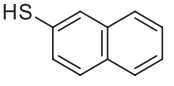
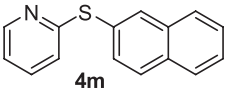
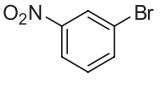
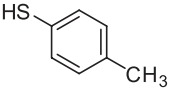
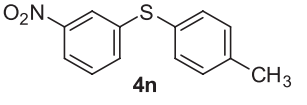
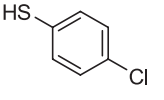
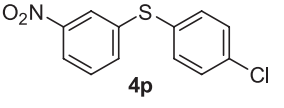
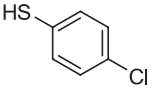
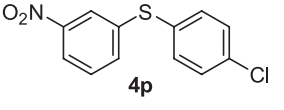
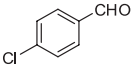
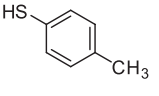
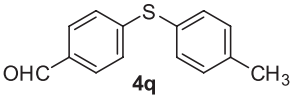
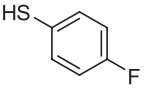
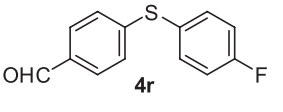
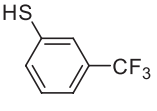
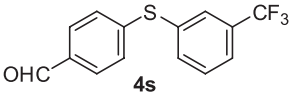
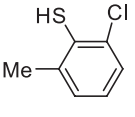
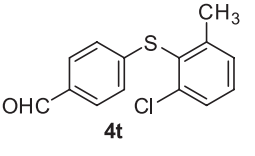
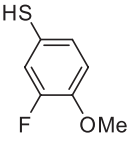
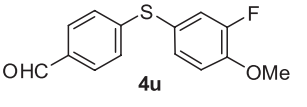
By using the same protocol, we were also able to couple aryl halides with various substituted thiophenols, and the results are summarized in Table 3. The substituted arylthiols were successfully coupled with the all aryl bromides and chlorides, and no significant electronic effects were

Table 3. Cross-coupling of thiophenol with aryl halides in the EtOH/K_3PO_4/water ATPS.[a]

Entry	Halides	Thiols	Aryl sulfides	Yield (%)[b]/time (h)
1			 **4a**	96/3
2			 **4b**	91/4
3			 **4c**	93/4
4			 **4d**	91/5
5			 **4e**	96/4
6			 **4f**	95/5
7			 **4g**	94/5
8			 **4h**	92/6
9			 **4i**	94/4
10			 **4j**	92/4
11			 **4k**	94/5

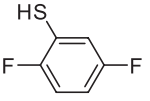
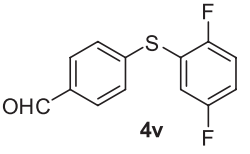
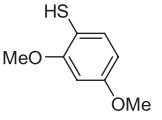
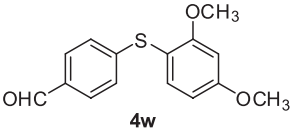
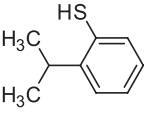
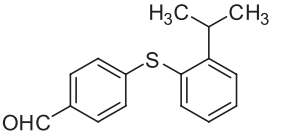
(*Continued*)

Table 3. *Continued*.

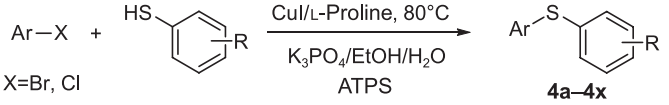
Entry	Halides	Thiols	Aryl sulfides	Yield (%)[b]/time (h)
12			 **4l**	82/8
13			 **4m**	84/8
14			 **4n**	97/2
15			 **4p**	96/4
16			 **4p**	93/4
17			 **4q**	85/6
18			 **4r**	96/8
19			 **4s**	89/8
20			 **4t**	86/8
21			 **4u**	96/6

(*Continued*)

Table 3. *Continued*.

Entry	Halides	Thiols	Aryl sulfides	Yield (%)[b]/time (h)
22			 **4v**	87/6
23			 **4w**	81/9
24			 **4x**	85/12

Notes: [a]Reaction conditions: thiophenol (5.5 mmol), halides (5 mmol), 5 mol% of CuI, 10 mol% of L-proline, 12 mmol of K_3PO_4, 6 ml of water and 4 ml of EtOH refluxed at 80 °C for 6 h in air atmosphere.
[b]Isolated yield (average of two runs).



Scheme 3. Reaction of thiols with chloro- and bromobenzene.

observed for *para*-substituted arylthiols when K_3PO_4 was used as a base in the aqueous two-phase media; *ortho*-substituted arylthiols typically gave a lower yield in the reaction (Entries 12, 20, 22, 23, and 24) (Scheme 3).

3. Conclusions

In summary, we have reported a practical, environmentally more friendly procedure for the copper-catalyzed S-arylation of thiols with aryl halides in the ATPS that proceeds to give good yields. The protocol is of potentially practical utility because of the low cost and the availability of aryl chlorides and the advantages associated with the use of water, but the reaction mechanism is not clear, maybe the specific interface action was the direct factor.

4. Experimental section

Materials and methods: all thiols (≥98%) were purchased from SHOU&FU Chemical company (www.shoufu.com); halides (99%) and CuI (99.99%) were purchased from Aldrich. NMR spectra (300 MHz for ^1H and 75 MHz for ^{13}C) were recorded with a Advance-300 Bruker spectrometer by using $CDCl_3$ as the solvent and Me_4Si as the internal standard. Flash column chromatography

was performed on silica gel (230–400 mesh) with ethyl acetate and hexane as eluents. Melting points were determined by using a Büchi B-540 melting point apparatus and are uncorrected.

4.1. *General procedure for the C–S cross-coupling reaction*

Thiophenol (5.5 mmol), halides (5 mmol), 5 mol% of CuI, 10 mol% of L-proline, and 12 mmol of K_3PO_4were added to in about 10 ml of the solvent (6 ml of water and 4 ml of EtOH) in air atmosphere, refluxed at 80 °C for the appropriate time, and monitored by TLC. Then the contents were cooled to room temperature and filtered, and H_2O (3 ml) and Et_2O (5 ml) were added. The aqueous layer was extracted using Et_2O (10 mL × 4). The combined organic layers were washed with saturated brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was further purified by column chromatography on silica (eluent: EtOAc/petroleum ether = 1:15) to afford the desired product.

4.2. *Data*

4.2.1. *Diphenyl sulfide (Table* 2*, Entry 1,* ***3a****)*

Colorless liquid (*26*) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (m, 2H), 7.19 (m, 4H), 7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 130.9, 129.1, 126.9.

4.2.2. *3-Nitrophenyl phenyl sulfide (Table* 2*, Entry 2,* ***3b****) (27)*

M.p.: 40–41 °C (Lit. 42 °C), ^{1}H NMR ($CDCl_3$): δ 7.16 (m, 3H), 7.38 (m, 3H), 7.67 (m, 1H), 7.85 (m, 1H), 8.12 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 147.0, 139.6, 135.2, 134.9, 131.2, 130.1, 129.1 (2C), 127.8, 123.5, 122.4.

4.2.3. *2-Phenylsulfanylpyridine (Table* 2*, Entry 3,* ***3c****)*

Colorless liquid (*28*). IR (neat): 3050, 1573, 1446, 1417, 1121, 752 cm^{-1}. GC-MS: (EI, *m*/*z*): 189 $[M+2]^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, J = 7.5 Hz, 1H), 6.96 (ddd, J = 1.1, 4.8, 7.4 Hz, 1H), 7.40 (m, 4 H), 7.58 (m, 2H), 8.39 (br d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.8, 121.3, 129.0, 129.6, 131.1, 134.9, 136.6, 149.5, 161.5.

4.2.4. *3-Chloro-2-phenylsulfanylpyridine (Table* 2*, Entry 4,* ***3d****)*

Light yellow oil (*29*). IR (KBr): 3053, 1560, 1477, 1387, 1151, 1026, 749 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (dd, J = 4.5, 7.5 Hz, 1H), 7.44 (m, 3H), 7.59 (m, 3H), 8.22 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.6, 123.2, 129.0, 129.1, 135.4, 136.2, 138.8, 147.3, 157.4.

4.2.5. *2-(Phenylthio)thiophene (Table* 2*, Entry 5,* ***3e****)*

Colorless oil (*26*). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.52 (dd, J = 4.1, 2H), 7.32 (m, 6H), 7.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.3, 125.9, 127.0, 127.9, 128.9, 131.2, 135.9, 138.6; Anal Calcd. for: C, 62.46; H, 4.19; S, 33.35. Found: C, 62.41; H, 4.15; S, 32.35.

4.2.6. *3-(Phenylthio)thiophene (Table* 2*, Entry 6,* ***3f)***

Colorless oil (*26*). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.62 (q, $J = 6.8$ Hz, 1H), 7.30 (m, 2H), 7.24 (m, 3H), 6.93 (d, $J = 5.6$ Hz, 1H), 6.76 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.5, 129.4, 129.0, 127.6, 127.4, 125.6, 125.2, 124.6; Anal calcd for: C, 62.46; H, 4.19; S, 33.35. Found : C, 62.41; H, 4.15; S, 32.35.

4.2.7. *4-(Phenylthio)benzonitrile (Table* 2*, Entry 7,* ***3g)***

White solid (*28*), m.p.: 52–53 °C. GC-MS: (EI, m/z): 211 (M^+); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (dd, $J = 8.7$, 3.0 Hz, 2H), 7.54 (m, 2H), 7.51–7.50 (m, 3H), 7.24 (dd, $J = 8.7$, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 134.7, 132.5, 131.0, 130.1, 129.6, 127.5, 119.0, 108.9.

4.2.8. *4-Methylphenyl phenyl sulfide (Table* 2*, Entry 8,* ***3h)***

A clear oil (*28*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 7.02 (d, $J = 7.9$, 2H), 7.19 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 137.1, 132.2, 131.2, 130.0, 129.7, 129.0, 126.4, 21.1.

4.2.9. *4,4-Dimethyl-6-(phenylthio)thiochromane (Table* 2*, Entry 8,* ***3i)***

Yellow crystals, m.p.: 81–83 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 6H) , 2.03 (m, 2H), 3.12 (m, 2H), 7.22 (d, $J = 6.4$ Hz, 1H), 7.38 (m, 2H), 7.49 (m, 2H), 7.62 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3, 141.2, 137.2, 131.1, 128.8, 127.3, 127.0, 126.8, 125.3, 124.9.

4.2.10. *4-(Phenylthio)benzaldehyde (Table* 2*, Entry 10,* ***3j)***

Yellow crystals (*30*), m.p.: 51–54 °C. IR (KBr): ν 2750, 1652, 1535, 785 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.25 (d, $J = 4.6$ Hz, 2H), 7.44 (m, 3H), 7.52 (m, 2H), 7.71 (q, $J = 8.6$ Hz, $J = 4.6$ Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 127.33, 129.15, 129.82, 130.13, 131.44, 133.82, 134.34, 147.19, 191.11.

4.2.11. *4-Benzotrifluoride(phenyl)sulfane (Table* 2*, Entry 11,* ***3k)***

A clear oil (*28*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.48 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$,) δ: 143.0, 133.6, 132.7, 129.9, 129.7, 128.7, 128.4, 126.1, 125.9.

4.2.12. *1-(4-(Phenylthio)phenyl)ethanone (Table* 2*, Entry 12,* ***3l)***

White solid (*29*), m.p.: 62–63.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.39 (m, 3H), 7.49 (m, 2H), 7.80 (d, $J = 8.4$ Hz, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 145.0, 134.7, 134.0, 132.3, 129.8, 129.1, 128.9, 127.7, 26.6.

4.2.13. *(4-nitrophenyl)(phenyl)sulfane (Table* 2*, Entry 13,* ***3m)***

Yellow solid (*28*), m.p.: 56–57 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (dd, $J = 9.2$, 2.3 Hz, 2H), 7.54 (m, 3H), 7.58 (d, $J = 2.8$ Hz, 2H), 8.13 (dd, $J = 9.2$, 2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.7, 145.5, 134.9, 130.5, 130.2, 129.9, 126.8, 124.2.

4.2.14. *4-Methoxyphenyl phenyl sulfide (Table* 3*, Entry 1,* ***4a****)*

Colorless liquid (*28*). ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H), 6.71 (d, $J = 8.8$ Hz, 2H), 6.98 (m, 3H), 7.04 (m, 2H), 7.23 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 138.5, 135.3 (2C), 128.8 (2C), 128.1 (2C), 125.7, 124.2, 114.9 (2C), 55.3.

4.2.15. *4-Methylphenyl phenyl sulfide (Table* 3*, Entry 2,* ***4b****)*

A clear oil (*31*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 7.02 (d, $J = 7.9$, 2H), 7.14 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.1, 132.2, 131.2, 130.0, 129.7, 129.0, 126.4, 21.1.

4.2.16. *3-Methylphenyl phenyl sulfide (Table* 3*, Entry 3,* ***4c****)*

Colorless liquid (*32*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 6.92 (m, 1H), 7.08 (m, 4H), 7.16 (m, 2H), 7.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 136.0, 135.1, 131.7, 130.6 (2C), 129.0 (2C), 128.9, 128.2, 127.9, 126.7, 21.2.

4.2.17. *(4-Isopropylphenyl)(phenyl)sulfane (Table* 3*, Entry 4,* ***4d****)*

Colorless liquid (*33*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, $J = 6.2$ Hz, 6H), 2.76–3.03 (m, 1H), 7.11–7.44 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 136.8, 131.9, 131.7, 130.0, 129.0, 128.1, 127.3, 127.1, 126.4, 33.7, 23.8.

4.2.18. *(4-Fluorophenyl)(phenyl)sulfide (Table* 3*, Entry 5,* ***4e****)*

Colorless liquid (*34*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (m, 2H), 7.21 (m, 1H), 7.26 (m, 4H), 7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.3 , 116.5, 126.7, 129.2 (2C), 129.9 (2C), 130.2, 134.0, 134.1, 136.6, 161.1, 163.6.

4.2.19. *(4-Chlorophenyl)(phenyl)sulfane (Table* 3*, Entry 6,* ***4f****)*

Colorless liquid (*35*). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, $J = 8.5$ Hz, 2H), 7.22–7.40 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): 135.4, 134.7, 132.1, 132.0, 131.4, 129.3, 127.5.

4.2.20. *(4-Bromophenyl)(phenyl)sulfane (Table* 3*, Entry 7,* ***4g****)*

Colorless liquid (*36*). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.38 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:135.0, 134.6, 132.9, 131.9, 131.2, 129.2, 127.4.

4.2.21. *(Naphthalen-6-yl)(phenyl)sulfane (Table* 3*, Entry 8,* ***4h****)*

Colorless liquid (*22*). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.05–7.58 (m, 8H), 7.62–7.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 133.7, 132.9, 132.2, 130.8, 129.8, 129.1, 128.8, 128.7, 127.6, 127.3, 127.0, 126.5, 126.1.

4.2.22. *2-p-Tolylsulfanylpyridine (Table* 3*, Entry 9,* ***4i****)*

Colorless liquid (*29*). IR (neat): 3042, 2920, 1571, 1448, 1417, 1123, 758 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 2.41 (s, 3H), 6.80 (d, $J = 7.4$ Hz, 1H), 6.92 (ddd, $J = 0.9, 4.8, 7.4$ Hz, 1H), 7.20 (d, $J = 7.8$ Hz, 2H), 7.38 (m, 1H), 7.47 (d, $J = 7.8$ Hz, 2H), 8.36 (br d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl3): d = 21.3, 119.5, 120.9, 127.2, 130.4, 135.2, 136.6, 139.4, 149.4, 162.1.

4.2.23. *2-(4-Bromophenylsulfanyl)pyridine (Table* 3*, Entry 10,* ***4j****)*

White solid (*29*), m.p.: 78–81 °C. IR (KBr): 3045, 1571, 1416, 1123, 1009, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, $J = 8.0$ Hz, 1H), 6.99 (ddd, $J = 0.8, 4.8, 7.4$ Hz, 1H), 7.38–7.47 (m, 3H), 7.53 (d, $J = 8.8$ Hz, 2H), 8.38 (br d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2, 121.6, 123.3, 130.2, 132.7, 136.1, 136.7, 149.6, 160.1. ESI MS: $m/z = 266$ (M + H).

4.2.24. *2-(4-Chlorophenylsulfanyl)pyridine (Table* 3*, Entry 11,* ***4k****)*

Light yellow liquid (*29*). IR (KBr): 3044, 1551, 1443, 1083, 816, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, $J = 8.0$ Hz, 1H), 6.98 (ddd, $J = 0.9, 4.8, 7.4$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.45 (m, 1H), 7.49 (d, $J = 8.3$ Hz, 2H), 8.37 (br d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2, 121.6, 129.8, 135.3, 136.0, 136.7, 149.7, 160.4.

4.2.25. *2-(2-Methoxyphenylsulfanyl)pyridine (Table* 3*, Entry 12,* ***4l****)*

Colorless liquid (*29*). IR (KBr): 2836, 1574, 1477, 1274, 1122, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.88–7.03 (m, 3H), 7.33–7.45 (m, 2H), 7.55 (m, 1H), 8.36 (br d, $J = 5.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 111.5, 119.5, 120.7, 121.3, 131.2, 136.4, 136.4, 136.9, 149.3, 159.6, 160.7.

4.2.26. *2-(Naphthalen-2-ylsulfanyl)pyridine (Table* 3*, Entry 13,* ***4m****)*

Light yellow oil (*29*). IR (KBr): 2922, 1570, 1447, 1414, 1121, 752 cm^{-1}. ^1H NMR (MHz, $CDCl_3$): δ 6.89 (d, $J = 7.8$ Hz, 1H), 6.96 (ddd, $J = 0.9, 4.8, 7.5$ Hz, 1H), 7.40 (m, 1H), 7.50 (m, 2H), 7.8 (d, $J = 8.4$ Hz, 1H), 7.77–7.88 (m, 3H), 8.11 (s, 1H), 8.40 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (MHz, $CDCl_3$): δ 119.9, 121.4, 126.6, 127.0, 127.8, 129.2, 133.8, 134.6, 134.5, 136.7, 149.5, 161.4.

4.2.27. *(3-Nitrophenyl)(p-tolyl)sulfane (Table* 3*, Entry 14,* ***4n****)*

White solid (*30*), m.p.: 108–110 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.39 (t, 1H), 8.17–8.20 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.44–7.54 (m, 3H), 7.31 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 137.7, 136.9, 130.8, 129.3, 127.5, 127.2, 126.7, 122.9, 122.2, 23.1.

4.2.28. *(4-Bromophenyl)(3-nitrophenyl)sulfane (Table* 3*, Entry 15,* ***4o****)*

White solid (*27*), m.p.: 132–134 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (t, 1H), 8.07 (dd, $J = 8.2$, 1.2 Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 1H), 7.71–7.79 (m, 2H), 7.45–7.54 (m, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 138.9, 135.8, 133.6, 132.3, 132.1, 128.0, 127.9, 122.0, 121.8.

4.2.29. *(4-Chlorophenyl)(3-nitrophenyl)sulfane (Table* 3*, Entry 16,* ***4p****)*

White solid (*31*), m.p.: 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (t, 1H), 8.03 (dd, J = 8.2, 1.2 Hz, 1H), 7.80–7.74 (m, 3H), 7.51 (t, 1H), 7.30–7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 139.9, 134.8, 133.8, 132.9, 130.7, 130.5, 129.9, 123.0, 122.6.

4.2.30. *4-(p-Tolylthio)benzaldehyde (Table* 3*, Entry 17,* ***4q****)*

Yellow solid (*30*), m.p.: 53–53 °C. IR (KBr): ν 2780, 1602, 1565, 785, 767 cm^{-1}. ^{1}H NMR ($CDCl_3$, MHz): δ 2.36 (s, 3H), 7.20 (m, 4H), 7.43 (dd, J = 8.0, 1.9 Hz, 2H), 7.70 (dd, J = 8.2 Hz, J = 1.7 Hz, 2H), 9.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 126.6, 128.5, 129.4, 129.8, 130.1, 130.6, 134.8, 139.7, 148.2, 191.1.

4.2.31. *4-(4-Fluorophenylthio)benzaldehyde (Table* 3*, Entry 18,* ***4r****)*

Yellow crystals (*30*), m.p.: 63–65 °C. IR (KBr): ν 2716, 1685, 1550 ,785 760 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (m, 4H), 7.22 (m, 2H), 7.32 (dt, J= 6.7 Hz, J = 1.8 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 116.9, 117.2, 126.7, 130.1, 133.8, 136.8, 136.9, 147.3, 161.8, 165.1, 191.0.

4.2.32. *4-(3-(Trifluoromethyl)phenylthio)benzaldehyde (Table* 3*, Entry 19,* ***4s****)*

Light yellow oil (*30*). ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.37 (dd, J= 8.8 Hz, J = 1.6 Hz, 2H), 7.56 (m, 1H), 7.66 (m, 2H), 7.77 (m, 3H), 9.94 (s, 1H); ^{13}C NMR (MHz, $CDCl_3$): 125.50, 128.53, 129.44, 129.90, 130.18, 130.48, 130.91, 133.89, 134.46, 136.53, 144.87, 191.17.

4.2.33. *4-(2-Chloro-6-methylphenylthio)benzaldehyde (Table* 3*, Entry 20,* ***4t****)*

White crystals (*30*), m.p.: 42–44 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 3H), 7.11 (dd, J = 6.8, 2.4 Hz, 2H), 7.34 (m, 2H), 7.45 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 8.3, 2.6 Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 20.1, 127.1, 129.7, 132.1, 132.1, 132.3, 133.9, 134.8, 140.3, 145.5, 190.9.

4.2.34. *4-(3-Fluoro-4-methoxyphenylthio)benzaldehyde (Table* 3*, Entry 21,* ***4u****)*

White solid (*30*), m.p.: 74–76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (s, 3H), 7.02 (t, J = 8.4 Hz, 1H), 7.17 (dd, J = 7.0, 2.6 Hz, 1H), 7.42 (m, 3H), 7.72 (dd, J = 6.9, 3.2 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 56.32, 114.24, 122.68, 126.51, 130.15, 131.67, 133.72, 147.60, 149.19, 150.84, 154.66, 191.09.

4.2.35. *4-(2,5-Difluorophenylthio)benzaldehyde (Table* 3*, Entry 22,* ***4v****)*

White solid (*30*), m.p.: 50–52 °C. ^{1}H NMR ($CDCl_3$, MHz): δ 7.19 (m, 3H), 7.34 (dd, J = 8.2, 3.2 Hz, 1H), 7.80 (dd, J = 6.7, 2.4 Hz, 2H), 9.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 117.20, 117.53, 117.92, 128.47, 130.32, 134.67, 143.28, 156.98, 160.25, 190.99.

4.2.36. *4-(2,4-Dimethoxyphenylthio)benzaldehyde (Table* 3*, Entry 23,* ***4w)***

White solid (*30*), m.p.: 124–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3H), 3.87 (s, 3H), 6.62 (m, 2H), 7.11 (dd, $J = 6.8, 4.8$ Hz, 2H), 7.53 (m, 1H), 7.74 (m, 2H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 55.56, 56.01, 99.58, 105.81, 125.49, 129.92, 133.15, 136.66, 148.37, 160.39, 161.28, 191.22.

4.2.37. *4-(2-Isopropylphenylthio)benzaldehyde (Table* 3*, Entry 24,* ***4x)***

Yellow oil (*30*). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (s, 3H), 1.20 (s, 3H), 3.58 (q, $J = 1.8$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.27 (m, 1H), 7.45 (d, $J = 4.2$ Hz, 2H), 7.52 (d, $J = 8.3$ Hz, 1H), 7.71 (d, $J = 8.3$ Hz, 2H), 9.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.74, 31.02, 126.52, 126.74, 127.14, 130.11, 130.48, 130.57, 133.37, 136.73, 148.38, 152.75, 191.20.

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