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Copper-Catalyzed C–S Cross-Coupling Reaction: S-Arylation of Arylthioureas

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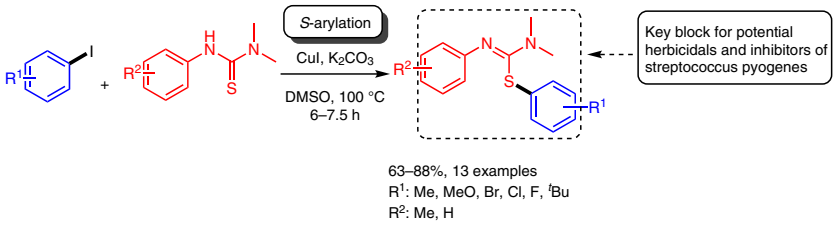

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Abstract A simple and efficient copper-catalyzed S-arylation of arylthioureas was developed. Arylthioureas were smoothly converted into aryl-isothioureas with good yield by copper-catalyzed S-arylation. The features of this method include the use of a ligand-free catalyst, good yield, short reaction time, and broad substrate scope. The method provides a facile and convenient preparation of some potentially biologically active compounds.

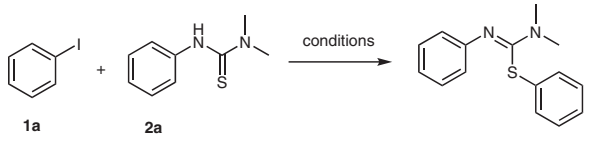
Key words copper, S-arylation, catalysis, thiourea, isothiourea

Aryl-isothiourea blocks are important functional groups with a wide range of applications in agrochemicals and drugs.[1–6] In the past decades, research on the application and synthesis of arylthioureas has attracted the attention of many biologists and chemists. Several methods have been reported for the synthesis of substituted aryl-isothioureas. For example, the reaction of aromatic thiols with amines,[7] isocyanates reacting with diazonium salts,[8] and the most widely used method is substituted arylthioureas reacting with amines, alkyl halides or benzensulfonic acid.[9–12] However, these methods suffer from restricted availability of substrates[8,9] and can produce mixtures of products.[10] As part of our longstanding interest in developing phenylthioureas and relevant applications,[13–17] herein we report a facile synthesis of aryl-isothioureas by a copper-catalyzed arylation reaction. In this work, substituted arylthioureas were converted into aryl-isothioureas catalyzed by CuI with good yields. The key grouping in the product (boxed in the graphic abstract) is known to be biologically active,[18,19] thus, the protocol might pave the way to the synthesis of a number of potentially pharmaceutically and biologically active molecules.

We began our investigations by using iodobenzene (**1a**) and arylthiourea **2a** as substrates to carry out the model reaction (Table 1). Optimization of the reaction conditions included screening of solvents, bases, catalysts, temperature, base loading, and catalyst loading. For the first trial, with no addition of catalyst, aryl-isothiourea could not be detected (entries 1–3), whereas the target compound was obtained when catalyst (CuI) was added (entry 4). It was found that the reaction was significantly affected by the nature of solvent, and high yield (90%) was obtained when dimethyl sulfoxide (DMSO) was used (entry 5). Subsequently, examination of base loading showed that increasing the amount of base to 2.5 equiv led to almost no yield change, whereas decreasing the base loading to 1.2 equiv led to a significant decrease in yield (entries 5–10). Among these, 1.7 equiv base loading was found to be optimal. Similarly, base screening showed that K_2CO_3 was the most suitable (entries 9, 11–13). It was noted that the catalyst loading of copper could be decreased to 0.05 equiv with almost no effect on the yield of the reaction (entry 14). Among the copper species surveyed, CuI was significantly superior to Cu_2O, CuBr, CuO, $CuCl_2$, $CoCl_2{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$, and $CuSO_4{\cdot}5H_2O$ (entries 15–21). Finally, decreasing the reaction temperature from 110 to 90 °C had a negative effect on the yield, whereas increasing the temperature to 120 °C made almost no difference (entries 22–24). The optimal reaction conditions are thus summarized in Table 1, entry 23.

By using the optimized reaction conditions, we further investigated the substrate scope of the C–S cross-coupling reaction, the results are summarized in Table 2. A range of substituted aryl iodides **1a–m** reacted with aryl-isothioureas **2a–b** giving the corresponding products in good yields. Aryl iodides bearing electron-withdrawing groups in the aryl rings (**1b**, **1c**, **1g**, and **1h**) were transformed into the corresponding products with good yields (entries 2, 3, 7, and 8), whereas electron-donating groups (**1d**, **1e**, **1f**, **1i**,

Table 1 Screening Reaction Conditions for S-Arylation Starting from Iodobenzene (**1a**) and Arylthiourea **2a**[a]



Entry	Catalyst (equiv)	Base (equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	–	NEt_3 (2.0)	THF	0	N.R
2	–	KOH (2.0)	DMSO	110	N.R
3	–	K_2CO_3 (2.0)	DMSO	110	N.R
4	CuI (0.2)	K_2CO_3 (2.0)	DMF	110	51
5	CuI (0.2)	K_2CO_3 (2.0)	DMSO	110	90
6	CuI (0.2)	K_2CO_3 (1.0)	DMSO	110	57
7	CuI (0.2)	K_2CO_3 (1.2)	DMSO	110	69
8	CuI (0.2)	K_2CO_3 (1.5)	DMSO	110	82
9	CuI (0.2)	K_2CO_3 (1.7)	DMSO	110	90
10	CuI (0.2)	K_2CO_3 (2.5)	DMSO	110	91
11	CuI (0.2)	KOH (1.7)	DMSO	110	23
12	CuI (0.2)	Cs_2CO_3 (1.7)	DMSO	110	89
13	CuI (0.2)	NEt_3 (1.7)	DMSO	110	32
14	CuI (0.05)	K_2CO_3 (1.7)	DMSO	110	90
15	Cu_2O (0.05)	K_2CO_3 (1.7)	DMSO	110	83
16	CuO (0.05)	K_2CO_3 (1.7)	DMSO	110	20
17	$CuCl_2$ (0.05)	K_2CO_3 (1.7)	DMSO	110	75
18	CuBr (0.05)	K_2CO_3 (1.7)	DMSO	110	84
19	$CoCl_2·6H_2O$ (0.05)	K_2CO_3 (1.7)	DMSO	110	N.R
20	$NiCl_2·6H_2O$ (0.05)	K_2CO_3 (1.7)	DMSO	110	N.R
21	$CuSO_4·5H_2O$ (0.05)	K_2CO_3 (1.7)	DMSO	110	42
22	CuI (0.05)	K_2CO_3 (1.7)	DMSO	90	58
23	**CuI (0.05)**	**K_2CO_3 (1.7)**	**DMSO**	**100**	**87**
24	CuI (0.05)	K_2CO_3 (1.7)	DMSO	120	91

[a] Reaction conditions: **1a** (1.2 mmol), **2a**(1.0 mmol), solvent (1.5 mL) for 6 h.
[b] Isolated yield.

and **1j**) attached to the aryl ring led to slightly reduced yields (entries 4–6 and 9–10). Subsequently, another arylthiourea **2b** was examined under the optimal conditions. We were pleased to find that arylthiourea **2b** was a good coupling partner to react with substituted aryl iodides, affording the corresponding products with reasonable yields (entries 11–13).

A tentative reaction mechanism is proposed (Scheme 1). Thiourea **2** could be transformed into isothiourea **B** in the presence of base. Iodobenzene (**1**) undergoes oxidative addition with CuI to give intermediate **A**, then transmetalation with isothiourea **B** gives intermediate **C**. Final reductive elimination from **C** furnishes the desired product **D**.

In conclusion, we have developed a simple and efficient copper-catalyzed S-arylation of thioureas. A variety of arylisothiourea derivatives are synthesized with good chemoselectivity and functional group tolerance. The protocol has practical synthetic value for the preparation of a number of biologically and pharmaceutically active compounds. Further details on the mechanism and relevant studies on dimethylphenylthioureas are under study in our laboratory.

All reactions were carried out under dried glassware fitted with septums. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. DMSO was dried with molecular sieves. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy and capillary GC analysis.

Preparation of *S*-Aryl Isothioureas in the Presence of CuI and K_2CO_3; Typical Procedure (TP)

In a dried tube, equipped with a magnetic stirrer and a septum, iodobenzene (1.2 mmol) was dissolved in DMSO (1.5 mL), then arylthiourea (1.0 mmol), CuI (0.05 mmol), and K_2CO_3 (1.5 mmol) were added. The mixture was stirred and heated at 100 °C and the progress of the reaction was monitored by TLC until the starting material was consumed (ca. 6–7.5 h). The mixture was cooled to r.t. and the reaction was quenched with sat. NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the organic extract was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography to afford the desired product.

1,1-Dimethyl-2,3-diphenyl-isothiourea (3a)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3a**.

Yield: 222.8 mg (87%); white solid; mp 65–67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.13 (m, 7 H), 6.90 (t, *J* = 7.66 Hz, 1 H), 6.72 (d, *J* = 7.54 Hz, 2 H), 3.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 150.7, 133.5, 130.3, 129.0, 128.4, 126.7, 122.3, 122.2, 39.8.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_2S$: 256.1034; found: 256.0954.

2-(4-Bromophenyl)-1,1-dimethyl-3-phenyl-isothiourea (3b)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3b**.

Yield: 293.9 mg (88%); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.22 Hz, 2 H), 7.12 (t, *J* = 7.90 Hz, 2 H), 6.89–6.98 (m, 3 H), 6.66–6.69 (m, 2 H), 3.07 (s, 6 H).

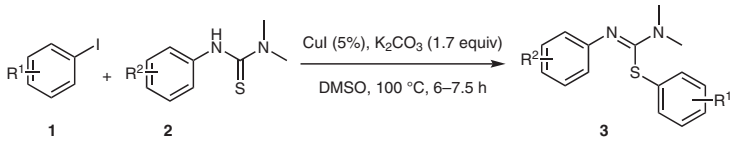
^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 150.3, 132.4, 132.1, 131.9, 128.4, 122.3, 122.2, 120.8, 39.8.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}BrN_2S$: 334.0139; found: 334.0144.

2-(4-Fluorophenyl)-1,1-dimethyl-3-phenyl-isothiourea (3c)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3c**.

Table 2 Copper-Catalyzed S-Arylation Starting from Iodobenzene (**1**) with Dimethylphenylthiourea (**2**)[a]



1 2 3

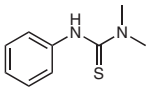
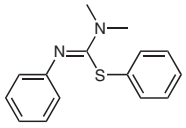
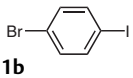
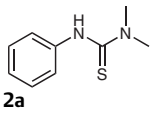
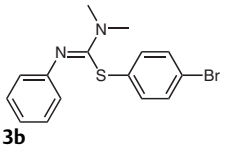
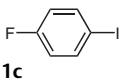
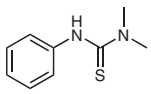
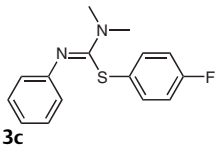
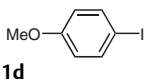
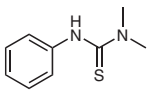
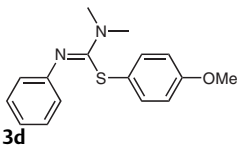
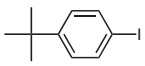
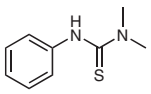
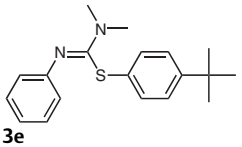
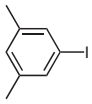
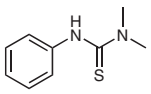
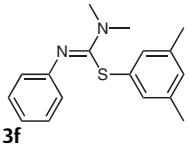
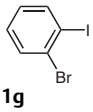
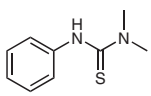
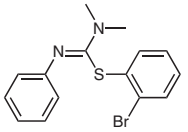
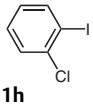
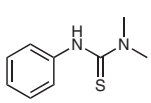
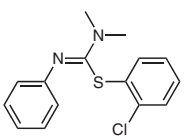
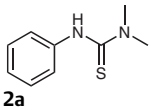
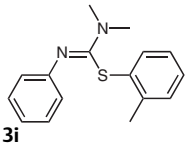
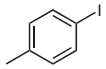
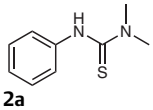
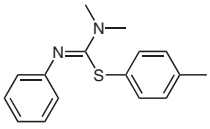
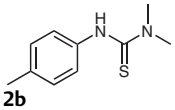
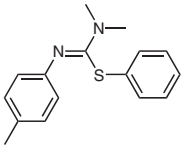
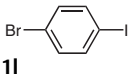
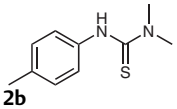
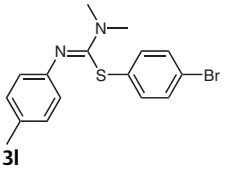
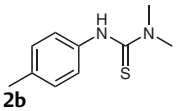
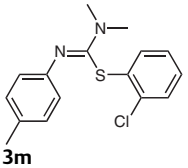
Entry	Aryl iodides	Arylisothioureas	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	87
2	 **1b**	 **2a**	 **3b**	88
3	 **1c**	 **2a**	 **3c**	78
4	 **1d**	 **2a**	 **3d**	66
5	 **1e**	 **2a**	 **3e**	63
6	 **1f**	 **2a**	 **3f**	70
7	 **1g**	 **2a**	 **3g**	76
8	 **1h**	 **2a**	 **3h**	73

Table 2 (continued)

Entry	Aryl iodides	Arylisothioureas	Product	Yield (%)[b]
9	 **1i**	 **2a**	 **3i**	72
10	 **1j**	 **2a**	 **3j**	75
11	 **1k**	 **2b**	 **3k**	76
12	 **1l**	 **2b**	 **3l**	78
13	 **1m**	 **2b**	 **3m**	70

[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), CuI (5 mol%), K_2CO_3 (1.7 mmol), and DMSO (1.5 mL), 100 °C, 6–7.5 h.

[b] Isolated yield.

Yield: 213.7 mg (78%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03–7.12 (m, 4 H), 6.79–6.90 (m, 3 H), 6.66 (d, *J* = 7.80 Hz, 2 H), 3.07 (s, 6 H).

^{13}CNMR (100 MHz, $CDCl_3$): δ = 161.9 (d, $^1J_{C-F}$=246 Hz), 153.4, 150.3, 133.2 (d, $^3J_{C-F}$=8 Hz), 128.3, 128.0 (d, $^4J_{C-F}$=2 Hz), 122.2, 122.1, 116.0 (d, $^2J_{C-F}$=22 Hz), 39.87.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}FN_2S$: 274.0940; found: 274.0932.

2-(4-Methoxyphenyl)-1,1-dimethyl-3-phenyl-isothiourea (3d)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3d**.

Yield: 188.8 mg (66%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 7.70 Hz, 2 H), 7.05 (d, *J* = 8.56 Hz,, 2 H), 6.91 (d, *J* = 7.42 Hz, 1 H), 6.68–6.72 (m, 4 H), 3.74 (s, 3 H), 3.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 154.5, 150.5, 133.1, 128.3, 123.4, 122.2, 122.0, 114.5, 55.3, 39.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2OS$: 286.1140; found: 286.1146.

2-(4-*tert*-Butylphenyl)-1,1-dimethyl-3-phenyl-isothiourea (3e)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3e**.

Yield: 196.6 mg (63%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–7.13 (m, 7 H), 6.71 (d, *J* = 7.74 Hz, 2 H), 3.06 (s, 6 H), 0.89–2.54 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 150.5, 141.4, 130.6, 129.7, 129.0, 128.3, 122.3, 122.1, 39.8, 35.2, 33.5, 22.2, 14.0.

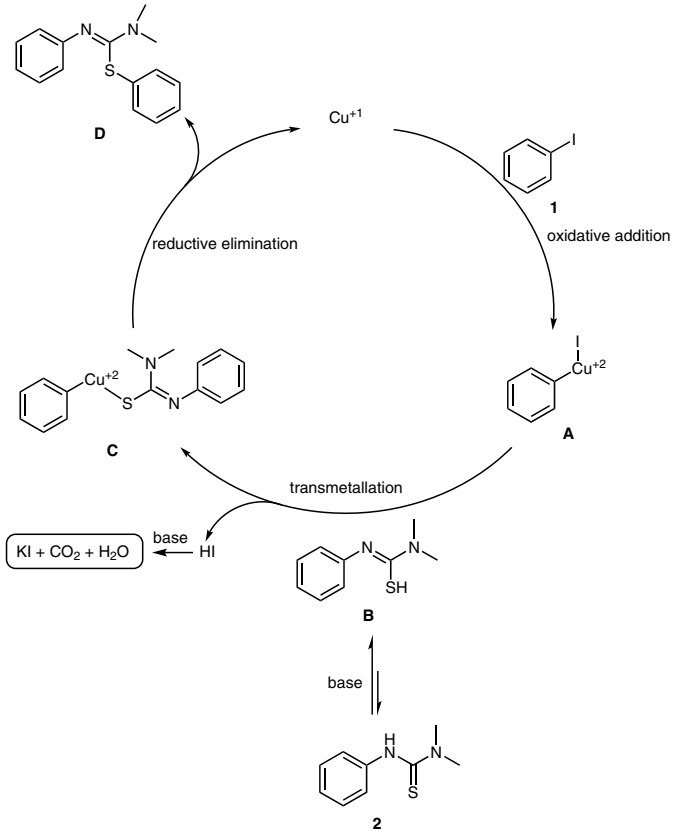
HRMS (ESI): *m*/*z* calcd for $C_{19}H_{24}N_2S$: 312.1660; found: 312.1651.

2-(3,5-Dimethylphenyl)-1,1-dimethyl-3-phenyl-isothiourea (3f)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3f**.

Yield: 198.8 mg (70%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (t, *J* = 7.80 Hz, 2 H), 6.70–6.91 (m, 6 H), 3.09 (s, 6 H), 2.19 (s, 6 H).



Scheme 1 Proposed mechanism for copper-catalyzed S-arylation

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.4, 138.5, 135.0, 132.5, 128.6, 128.2, 122.3, 122.0, 39.8, 21.2.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{20}N_2S$: 284.1347; found: 284.1354.

2-(2-Bromophenyl)-1,1-dimethyl-3-phenyl-isothiourea (3g)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3g**.

Yield: 253.8 mg (76%); white solid; mp 70–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.24 Hz, 1 H), 7.03–7.14 (m, 4 H), 6.85–6.96 (m, 2 H), 6.70 (d, *J* = 7.80 Hz, 2 H), 3.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 150.2, 134.3, 132.9, 132.5, 128.3, 128.1, 127.7, 124.9, 122.2, 122.0, 39.8.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}BrN_2S$: 334.0139; found: 334.0149.

2-(2-Chlorophenyl)-1,1-dimethyl-3-phenyl-isothiourea (3h)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3h**.

Yield: 211.7 mg (73%); white solid; mp 58–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.23 (m, 1 H), 6.95–7.10 (m, 5 H), 6.86 (t, *J* = 7.31 Hz, 1 H), 6.68 (d, *J* = 7.31 Hz, 2 H), 3.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 150.2, 134.8, 132.8, 132.1, 129.6, 128.3, 128.1, 127.0, 122.2, 121.9, 39.8.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}ClN_2S$: 290.0644; found: 290.0651.

1,1-Dimethyl-3-phenyl-2-*o*-tolyl-isothiourea (3i)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3i**.

Yield: 194.5 mg (72%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96–7.13 (m, 6 H), 6.86 (d, *J* = 7.16 Hz, 1 H), 6.68 (d, *J* = 7.38 Hz, 2 H), 3.04 (s, 6 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 150.6, 138.4, 132.4, 131.7, 130.2, 128.3, 127.2, 126.5, 122.1, 122.0, 39.7, 20.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2S$: 270.1191; found: 270.1199.

1,1-Dimethyl-3-phenyl-2-*p*-tolyl-isothiourea (3j)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3j**.

Yield: 202.5 mg (75%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 8.02 Hz, 2 H), 6.98–7.05 (m, 4 H), 6.92 (t, *J* = 7.18 Hz, 1 H), 6.73 (d, *J* = 7.82 Hz, 2 H), 3.06 (s, 6 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 150.5, 136.7, 130.5, 129.7, 129.7, 128.3, 122.3, 122.2, 39.8, 21.1.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2S$: 270.1191; found: 270.1199.

1,1-Dimethyl-2-phenyl-3-*p*-tolyl-isothiourea (3k)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3k**.

Yield: 205.3 mg (76%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.21 (m, 5 H), 6.97 (d, *J* = 7.40 Hz, 2 H), 6.65 (d, *J* = 8.17 Hz, 2 H), 3.05 (s, 6 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 147.9, 133.7, 131.7, 130.0, 129.0, 128.9, 126.6, 122.0, 39.8, 20.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2S$: 270.1191; found: 270.1195.

2-(4-Bromophenyl)-1,1-dimethyl-3-*p*-tolyl-isothiourea (3l)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3l**.

Yield: 272.2 mg (78%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.32 Hz, 2 H), 6.95–7.01 (m, 4 H), 6.60 (d, *J* = 7.52 Hz, 2 H), 3.05 (s, 6 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 147.8, 132.7, 131.9, 131.7, 131.8, 129.0, 121.9, 120.7, 39.8, 20.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}BrN_2S$: 348.0296; found: 348.0301.

2-(2-Chlorophenyl)-1,1-dimethyl-3-*p*-tolyl-isothiourea (3m)

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 13:1) to give the target compound **3m**.

Yield: 202.8 mg (70%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 7.48 Hz, 1 H), 7.00–7.13 (m, 3 H), 6.91 (d, *J* = 7.78 Hz, 2 H), 6.61 (d, *J* = 8.22 Hz, 2 H), 3.05 (s, 6 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 147.8, 134.6, 132.4, 131.5, 129.6, 129.0, 128.0, 127.0, 121.8, 39.7, 20.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}ClN_2S$: 304.0801; found: 304.0809.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590879.

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