EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901401

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901401

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10.1002/ejoc.201901401

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Chemo-selective C-S/S-S Formation between Diaryl Disulfides and Tetraalkylthiuram Disulfides

Kang Peng,[a] Hui Zhu,[a] Xing Liu,[a] Han-Ying Peng, [a] Jin-Quan Chen,[a] and Zhi-Bing Dong* [a],[b],[c]

Abstract: An efficient C-S/S-S formation for the chemo-selective synthesis of aryl dithiocarbamate (C-S formation) and aryl dialkylcarbamo(dithioperoxo)thioate (S-S formation) was studied. The chemo-selectivity could be controlled by modulating the reaction temperature, base, and catalyst. The transformation features simple performance, easily available starting material, high selectivity and easy performance, showing its practical synthetic value for the preparation of some potential biologically or pharmaceutically active compounds.

Introduction

Organosulfur compounds are widely used in medicines, pesticides and biological study.[1] Among these, dithiocarbamate derivatives have become the focus of research interest due to their significant biological activity.[2] Many compounds containing this skeleton have been reported to be biologically active, such as monoacylglycerol lipase inhibitors (**a, c**),[3] leukemic cells inhibitors,[4] thymocytes inhibitors,[5] antitumor agents,[6] and antibacterial agents (Figure 1).[7] In addition, they are an important class of versatile synthetic intermediates in organic synthesis,[8] they have also been used as linkers in solid-phase organic synthesis,[9] as protection groups in peptide synthesis,[10] and recently in the synthesis of ionic liquids.[11] Moreover, dialkylcarbamo(dithioperoxo)thioates are reported to show anti-filarial activities (**b**) (Figure 1).[12]

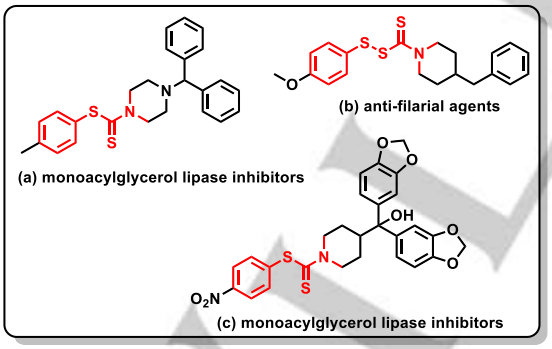


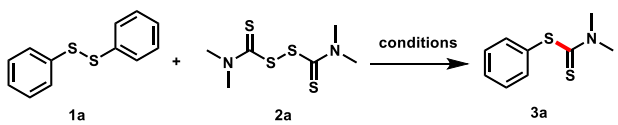
Figure 1. Representative organic dithiocarbamates with biological activity.

So far, a variety of methods are successfully employed for the synthesis of aryl dithiocarbamates, while there are very few reports for the synthesis of dialkylcarbamo(dithioperoxo)thioate.[13] Typical approaches to aryl dithiocarbamates involve the coupling reaction of one-pot three-component reactions using amines and carbon disulfide with electrophiles, including alkyl[14] or aryl halides,[15] arenediazonium fluoroborates,[16] N-(phenylthio)phthalimide[17] and arylboronic acids.[18] Although remarkable progress has been made, these methods are still limited by tedious operation steps, flammable and explosive substrates or reagents, and high substrate molar ratios. Therefore, it would be still attractive to explore more effective and mild methods, especially the ones starting from easily available materials and inexpensive catalysts. As part of our longstanding interest in developing organosulfur chemistry and exploring their relevant applications,[19] we report here a protocol for the selective synthesis of dithiocarbamates (C-S formation) and aryl dialkylcarbamo(dithioperoxo)thioates (S-S formation) starting from diaryl disulfides and tetraalkylthiuram disulfides (TATD). The synthesis selectivity could be controlled by modulating the reaction temperature, base, and catalyst. It is worthy to note that the efficiency and easy performance make the protocol attractive for the selective preparation of *S*-arylated or *S*-*S*-arylated dithiocarbamates.

Results and Discussion

Diphenyl disulfide (**1a**) and tetramethylthiuram disulfide (TMTD, **2a**) were selected as the starting materials to explore the possible C-S/S-S formation, the isolated yields were calculated based on PhS group since both substrates are symmetrical disulfides. Gratifyingly, the desired product aryl dithiocarbamates (**3a**) was obtained in 42% yield when the reaction was conducted in the presence of K_2CO_3 in DMF at 120 °C (Table 1, entry 1). To optimize the synthesis conditions of *S*-aryl dithiocarbamate (C-S formation), the effect of bases were evaluated (entries 2−4), and K_2CO_3 was proved to be the optimal. The examination of solvents (entries 1, 5-7) and reaction temperature (entries 1, 8-10) showed that N, N-dimethylformamide (DMF) was the best solvent, 120 °C was the optimal reaction temperature. By increasing the base loading did not promote the yield (entry 11-12), and the addition of a catalyst showed a slight yield increase (entry 13). Encouraged by these results, several transition metal catalysts were surveyed (entries 14-26), and the best one was CuI (10 mol% yields in 65%). Thus, the optimized reaction conditions were summarized as follows, diphenyl disulfide (**1a**, 1 mmol) and tetramethylthiuram disulfide (**2a**, 1.2 mmol), CuI (10 mol %) and K_2CO_3 (2.0 eq.) in DMF (2 mL) at 120 °C for 24 hours (entry 25).

Table 1. Optimization of reaction conditions for the synthesis of **3a**[a]



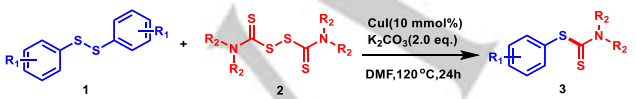
[a] School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430205, China.
[b] Key Laboratory of Green Chemical Process, Ministry of Education, Wuhan Institute of Technology, Wuhan 430205, China
[c] Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University, Wuhan 430062, China.
Email: dzb04982@wit.edu.cn
https://cee.wit.edu.cn/info/1052/1538.htm

Entry	Catalyst (mol%)	Base	Solvent	Temp[°C]	Yield (%)[b]
1	-	K_2CO_3	DMF	120	42
2	-	Cs_2CO_3	DMF	120	31
3	-	Na_2CO_3	DMF	120	27
4	-	t-BuOK	DMF	120	36
5	-	K_2CO_3	DMAc	120	Less
6	-	K_2CO_3	DMSO	120	31
7	-	K_2CO_3	Toluene	120	N.R.
8	-	K_2CO_3	DMF	80	24
9	-	K_2CO_3	DMF	100	35
10	-	K_2CO_3	DMF	130	41
11[c]	-	K_2CO_3	DMF	120	40
12[d]	-	K_2CO_3	DMF	120	41
13	$PdCl_2$(20)	K_2CO_3	DMF	120	48
14	$PdBr_2$(20)	K_2CO_3	DMF	120	40
15	$NiCl_2$(20)	K_2CO_3	DMF	120	29
16	$CuCl_2$(20)	K_2CO_3	DMF	120	27
17	Cu_2O(20)	K_2CO_3	DMF	120	52
18	CuI(20)	K_2CO_3	DMF	120	64
19	CuBr(20)	K_2CO_3	DMF	120	53
20	$PdCl_2$(10)	K_2CO_3	DMF	120	42
21	$NiBr_2$(10)	K_2CO_3	DMF	120	53
22	$CoBr_2$(10)	K_2CO_3	DMF	120	54
23	$Pd(OAc)_2$(10)	K_2CO_3	DMF	120	37
24	Cu_2O(10)	K_2CO_3	DMF	120	39
25	**CuI(10)**	**K_2CO_3**	**DMF**	**120**	**65**
26	CuBr(10)	K_2CO_3	DMF	120	42

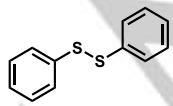
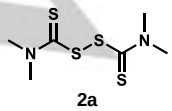
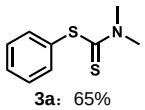
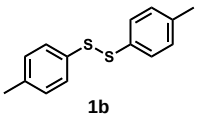
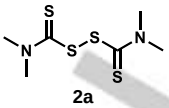
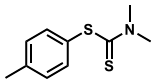
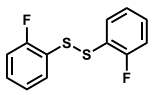
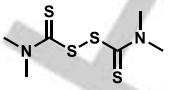
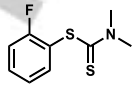
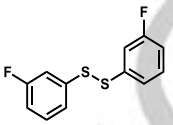
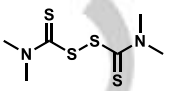
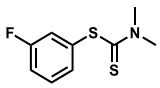
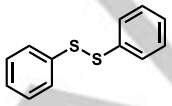
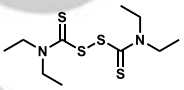
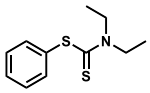
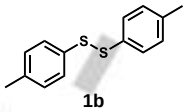
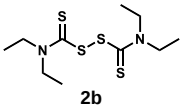
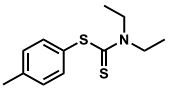
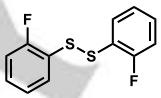
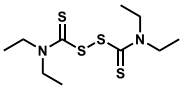
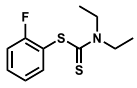
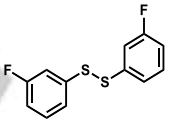
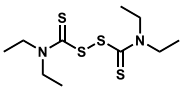
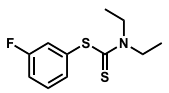
[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (mol%), base (2.0 equiv), solvent (2 mL), stirred for 24 hours. [b] Isolated yields based on PhS group. [c] Base (3.0 equiv). [d] Base (4.0 equiv).

With the optimal reaction conditions in hand, the substrate scope was investigated. As shown in Table 2, a variety of substituted diphenyl disulfides reacted with tetraalkylthiuram disulfides (**2**, TATD), giving the desired products with moderate to good yields (Table 2, entries 1-8). Electron-donating groups attached to the aryl ring of diphenyl disulfides promoted the reaction slightly (entry 2). Electron-withdrawing groups deactivated the diphenyl disulfides, providing the products in lower yields (entries 3-4). In addition, tetraethylthiuram disulfide (**2b**, TETD) was also suitable for C-S formation under standard reaction conditions. The corresponding products were obtained in slightly lower yields due to the possible steric hindrance from the alkyl group of the tetraethylthiuram disulfides (entries 5-8). The yields of aryl dithiocarbamates obtained by using this protocol are lower than our previous ones,[18d-18h] while it might offer an alternative way for the construction of these important compounds.

Table 2. Substrate scope for the synthesis of aryl dithiocarbamates **3**[a]



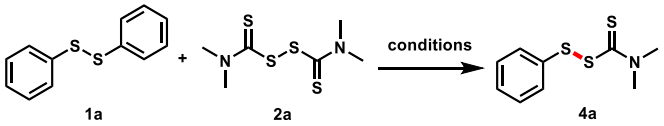
1 2 3

Entry	Diphenyl disulfide	Tetraalkylthiuram disulfide	Product Yield(%)[b]
1	 **1a**	 **2a**	 **3a**: 65%
2	 **1b**	 **2a**	 **3b**: 66%
3	 **1c**	 **2a**	 **3c**: 52%
4	 **1d**	 **2a**	 **3d**: 49%
5	 **1a**	 **2b**	 **3e**: 57%
6	 **1b**	 **2b**	 **3f**: 59%
7	 **1c**	 **2b**	 **3g**: 55%
8	 **1d**	 **2b**	 **3h**: 47%

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), CuI (10 mmol%), K_2CO_3 (2.0 equiv), DMF (2 mL), stirred at 120℃ for 24 hours. [b] Isolated yields based on PhS group.

To our delight, when the temperature dropped to 60 °C, the S-S bond formation product dimethylcarbamo(dithioperoxo)thioate (**4a**) was produced (Table 3, entry 1) under the above standard reaction conditions, and the yield could be increased to 40% when the model reaction was conducted at room temperature (entry 2). Several different catalysts were subsequently tried，and no significant yields increase were found (entries 3-6). With no addition of catalyst or base, the yield dropped slightly (entries 7−8), which indicated that the base or catalyst was not crucial for the reaction. The solvents screening showed that DMF afforded the best result (entries 9-15). Lastly, the substrate ratio of **1a** to **2a** was examined (entries 5, 16-17), and it turned out that the optimal ratio (**1a**:**2a**) was 1:1.2 (entry 16). The optimal reaction conditions for the synthesis of aryl dialkylcarbamo(dithioperoxo)thioate are summarized in entry 16.

Table 3. Optimization of reaction conditions for the synthesis of **4a**[a]

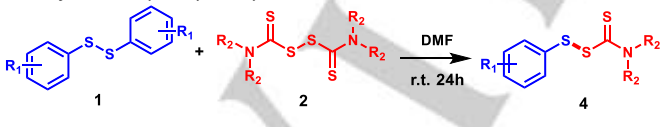


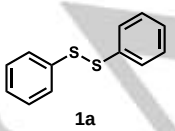
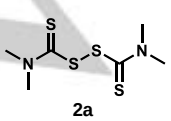
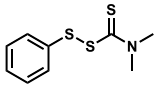
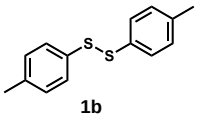
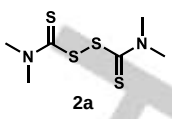
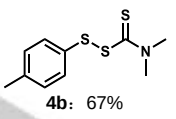
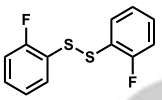
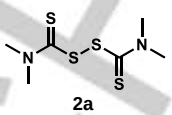
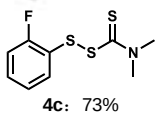
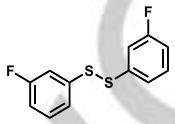
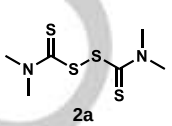
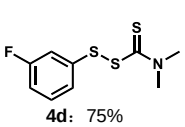
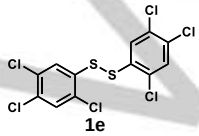
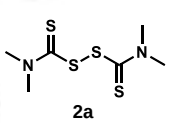
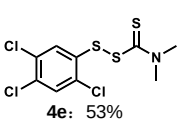
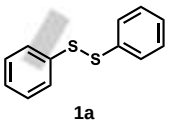
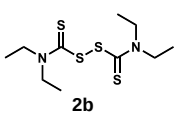
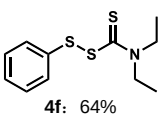
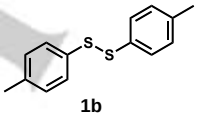
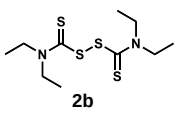
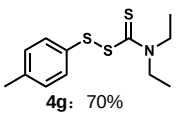
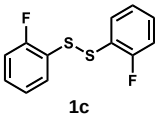
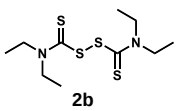
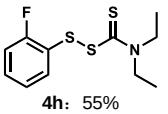
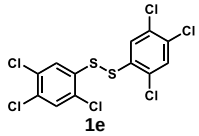
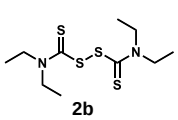
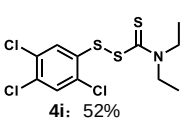
Entry	Catalyst	Base	Solvent	Temp[°C]	Yield (%)[b]
1	CuI	K_2CO_3	DMF	60	31
2	CuI	K_2CO_3	DMF	r. t.	40
3	$PdCl_2$	K_2CO_3	DMF	r. t.	52
4	$Cu(OAc)_2$	K_2CO_3	DMF	r. t.	51
5	$NiBr_2$	K_2CO_3	DMF	r. t.	41
6	$CoBr_2$	K_2CO_3	DMF	r. t.	48
7	-	K_2CO_3	DMF	r. t.	47
8	$PdCl_2$	-	DMF	r. t.	48
9	-	-	DMF	r. t.	54
10	-	-	CH_2Cl_2	r. t.	N.R.
11	-	-	MeCN	r. t.	Less
12	-	-	DMSO	r. t.	53
13	-	-	1,4-Dioxane	r. t.	N.R.
14	-	-	Toluene	r. t.	N.R.
15	-	-	Acetone	r. t.	Mess
16[c]	**-**	**-**	**DMF**	**r. t.**	**66**
17[d]	-	-	DMF	r. t.	61

[a] Reaction conditions (for entries 1–12): **1a** (1 mmol), **2a** (1 mmol), catalyst (10 mol%), base (2.0 equiv),solvent(2 mL), stirred for 24 hours. [b] Isolated yields based on PhS group. [c]: **1a** (1 mmol), **2a** (1.2 mmol). [d]: **1a** (1 mmol), **2a** (1.5 mmol).

Under the optimized reaction conditions, the scope of the substrates for the synthesis of aryl dialkylcarbamo(dithioperoxo)thioates was investigated (Table 4). In general, the substituted diphenyl disulfides reacted well with tetraalkylthiuram disulfides, furnishing aryl dialkylcarbamo(dithioperoxo)thioates in moderate to good yields. To our delight, diphenyl disulfides bearing electron-withdrawing groups such as F gave the products in good yields (entry 3-4). Diphenyl disulfides bearing multiple electron-withdrawing groups such as Cl gave the products in moderate yields (entries 5 and 9). Generally, due to the possible steric hindrance from the alkyl group of the tetraethylthiuram disulfides, the corresponding products were obtained in slightly lower yields (entries 6-9).

Table 4. Substrate scope for the synthesis of aryl dimethylcarbamo(dithioperoxo)thioates **4**[a]



Entry	Diphenyl disulfide	Tetraalkylthiuram disulfide	Product Yield (%)[b]
1	 1a	 2a	 **4a**: 66%
2	 1b	 2a	 **4b**: 67%
3	 1c	 2a	 **4c**: 73%
4	 1d	 2a	 **4d**: 75%
5	 1e	 2a	 **4e**: 53%
6	 1a	 2b	 **4f**: 64%
7	 1b	 2b	 **4g**: 70%
8	 1c	 2b	 **4h**: 55%
9	 1e	 2b	 **4i**: 52%

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), DMF (2 mL), stirred at r. t. for 24 hours. [b] Isolated yields based on PhS group.

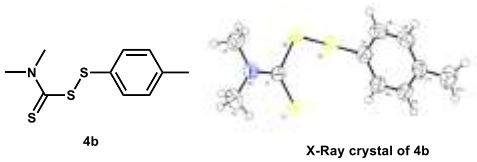


Figure 2. X-ray crystallography of S-S bond formation product **4b**.

To further confirm the S-S bond formation, the product **4b** was characterized by X-ray crystallography (Figure 2, CCDC 1962450).

Conclusions

In summary, an efficient C-S/S-S formation for the chemo-selective synthesis of aryl dithiocarbamates and aryl dialkylcarbamo(dithioperoxo)thioates was reported. The approach uses inexpensive and readily available diphenyl disulfides and tetramethyl thiuram disulfides as starting materials, a series of 17 aryl dithiocarbamates and aryl dimethylcarbamo(dithioperoxo)thioates could be furnished smoothly in moderate to good yields by modulating the reaction temperature, base, and catalyst. The protocol features easily available starting materials, high selectivity and easy performance, showing its practical synthetic value for the preparation of some potential biologically or pharmaceutically active compounds. The reaction mechanism and the related applications of this protocol are under investigation in our laboratory.

Experimental Section

General remarks: All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC analysis. NMR spectra were recorded on a Bruker AM400 NMR instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in ppm, and coupling constants (*J*) are given in Hz. All melting points were determined on an RY-1G melting point instrument without correction. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan 90 mass instrument (ESI). TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and visualized with UV light at 254 nm. Column chromatography was performed on silica gel (200−300 mesh) with PE (petroleum ether)/EtOAc as an eluent.

Typical procedure for the preparation of aryl dithiocarbamate (TP1): diphenyl disulfide (1 mmol), tetraalkylthiuram disulfide (1.2 mmol), CuI (10 mmol %) and K_2CO_3 (2.0 mmol) were added in a dried sealed tube equipped with a septum and magnetic stirring bar, DMF (2.0 mL) was then added. The mixture was stirred at 120 ℃ and checked by TLC until the starting material was finished (about 24 h). The reaction was quenched with sat. NH_4Cl solution (3.0 mL) and then extracted with ethyl acetate. The crude solution was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography to afford the desired product.

Typical procedure for the preparation of dimethylcarbamo(dithioperoxo)thioate (TP2): diphenyl disulfide (1 mmol) and tetraalkylthiuram disulfide (1.2 mmol) were added in a dried sealed tube equipped with a septum and magnetic stirring bar, DMF (2.0 mL) was then added. The mixture was stirred at room temperature and checked by TLC until the starting material was finished (about 24 h). The reaction was quenched with sat. NH_4Cl solution (3.0 mL) and then extracted with ethyl acetate. The crude solution was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography to afford the desired product.

Phenyl dimethylcarbamodithioate (3a)[19f]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3a** 256 mg (yield: 65 %), a white solid. M.p.: 90-92 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55-7.48 (m, 5H), 3.54 (s, 3H), 3.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 137.1, 131.9, 130.1, 129.2, 45.8, 42.2 ppm. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{12}NS_2$ (198.0406); found: 198.0409.

4-Methylphenyl dimethylcarbamodithioate (3b)[19f]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3b** 279 mg (yield: 66 %), a white solid. M.p.: 110-112 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* =8.0 Hz, 2H), 3.58 (s, 3H), 3.52 (s, 3H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 140.4, 131.9, 136.8, 128.3, 45.7, 42.0, 21.5 ppm. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{10}H_{14}NS_2$ (212.0562); found: 212.0567.

2-Fluorophenyl dimethylcarbamodithioate (3c)[20a]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3c** 224 mg (yield: 52 %), a white solid. M.p.: 150-152 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55-7.46 (m, 2H), 7.27-7.20 (m, 2H), 3.56 (s, 3H), 3.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 163.2 (d, $J_{C\text{-}F}$ = 249Hz), 138.6, 133.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 127.8 (d, $J_{C\text{-}F}$ = 4.0 Hz), 119.3 (d, $J_{C\text{-}F}$ = 17.0 Hz), 116.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 45.8, 42.4 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -105.5 (s, 1F). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{11}FNS_2$ (216.0312); found: 216.0315.

3-Fluorophenyl dimethylcarbamodithioate (3d)[20a]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3d** 211 mg (yield: 49 %), a pale yellow solid. M.p.: 52-56 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.40 (m, 1H), 7.30-7.17 (m, 3H), 3.57 (s, 3H), 3.50 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4, 162.5 (d, $J_{C\text{-}F}$ = 247.0 Hz), 133.3, 132.7 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 123.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 117.2 (d, $J_{C\text{-}F}$ = 21.0 Hz), 45.7, 42.1 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -111.8 (s, 1F). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_9H_{11}FNS_2$ (216.0312); found: 216.0309.

Phenyl diethylcarbamodithioate (3e)[19f]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3e** 257 mg (yield: 57 %), a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.48 (d, J = 9.0 Hz, 5H), 4.06 (d, *J* = 6.0 Hz, 2H), 3.89 (d, *J* = 3.0 Hz, 2H), 1.43 (t, *J* = 3.0 Hz, 3H), 1.32 (t, *J* = 4.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 137.1, 131.6, 130.0, 129.0, 49.9, 47.3, 12.7, 11.6 ppm. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{16}NS_2$ (226.0719); found: 226.0723.

4-Methylphenyl diethylcarbamodithioate (3f)[19f]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3f** 282 mg (yield: 59 %), a white solid. M.p.: 73-75 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.39 (d, *J* = 2.0 Hz, 2 H), 7.28 (d, *J* = 2.0 Hz, 2H), 4.09-4.03 (m, 2H), 3.91-3.96 (m, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 4.0 Hz, 3H), 1.31 (t, *J* = 3.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5, 140.3, 137.0, 129.9, 128.2, 49.9, 47.2, 21.5, 12.7, 11.6 ppm. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{18}NS_2$ (240.0875); found: 240.0879.

2-Fluorophenyl diethylcarbamodithioate (3g)[18]: According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3g** 267 mg (yield: 55 %), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55-7.47 (m, 2H), 7.29-7.19 (m, 2H), 4.07-4.02 (, 2H), 3.93-3.88 (m, 2H), 1.45 (t, *J* = 4.0 Hz, 3H), 1.31 (t, *J* = 3.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 163.2 (d, $J_{C\text{-}F}$ = 249.0 Hz), 138.8, 133.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 124.6 (d, $J_{C\text{-}F}$ = 4.0 Hz), 119.2 (d, $J_{C\text{-}F}$ = 18.0 Hz), 116.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 50.1, 47.1,

12.8, 11.6 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -105.3 (s, 1F). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}FNS_2$ (244.0625); found: 244.0621.

3-Fluorophenyl diethylcarbamodithioate (3h): According to TP1, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3h** 228 mg (yield: 47 %), a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.40 (m, 1H), 7.32-7.18 (m, 3H), 4.08-4.03 (m, 2H), 3.90-3.85 (m, 2H), 1.43 (t, *J* = 5.0 Hz, 3H), 1.32 (t, *J* = 3.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 162.4 (d, $J_{C\text{-}F}$ = 247.0 Hz), 133.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 132.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 117.2 (d, $J_{C\text{-}F}$ = 21.0 Hz), 49.9, 47.5, 12.8, 11.6 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -120.0 (s, 1F). HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{11}H_{15}FNS_2$ (244.0625); found: 244.0627.

Phenyl dimethylcarbamo(dithioperoxo)thioate (4a)[17]: According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **4a** 302 mg (yield: 66 %), a white solid. M.p.: 68-70 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.25 (m, 5H), 3.58 (s, 3H), 3.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.7, 135.9, 129.3, 128.9, 128.0, 47.5, 41.8 ppm. Anal. calcd for $C_9H_{11}NS_3$: C, 47.13; H, 4.83; N, 6.11; found: C, 47.01; H, 4.95; N, 6.02%.

4-Methylphenyl dimethylcarbamo(dithioperoxo)thioate (4b)[20b]: According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **4b** 327 mg (yield: 67 %), a white solid. M.p.: 79-81 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 2.0 Hz, 2H), 7.10 (d, *J* =2.0 Hz, 2H), 3.56 (s, 3H), 3.41 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 138.4, 132.5, 130.2, 129.7, 47.4, 41.7, 21.7 ppm. Anal. calcd for $C_{10}H_{13}NS_3$: C, 49.35; H, 5.38; N, 5.75; found: C, 49.21; H, 5.47; N, 5.68%.

2-Fluorophenyl dimethylcarbamo(dithioperoxo)thioate (4c): According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **4c** 361 mg (yield: 73 %), a yellow solid. M.p.: 50-52 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69-7.53 (m, 1H), 7.27-7.25 (m, 1H), 7.14-7.03 (m, 2H), 3.59 (s, 3H), 3.47 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 160.6 (d, $J_{C\text{-}F}$ = 246 Hz), 132.0 (d, $J_{C\text{-}F}$ = 1.0 Hz), 130.0 (d, $J_{C\text{-}F}$ = 7.0 Hz), 124.5 (d, $J_{C\text{-}F}$ = 4.0 Hz), 122.7, 115.6 (d, $J_{C\text{-}F}$ = 21.0 Hz), 47.4, 41.7 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -109.9 (s, 1F). Anal. calcd for $C_9H_{10}NS_3$: C, 43.70; H, 4.07; N, 5.66; found: C, 43.54; H, 4.19; N, 5.55%.

3-Fluorophenyl dimethylcarbamo(dithioperoxo)thioate (4d): According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **4d** 371 mg (yield: 75 %), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.24 (m, 3H), 6.95-6.90 (m, 1H), 3.58 (s, 3H), 3.47 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 162.7 (d, $J_{C\text{-}F}$ = 247.0 Hz), 138.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 115.4 (d, $J_{C\text{-}F}$ = 24.0 Hz), 114.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 45.6, 41.7 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -111.1 (s, 1F). Anal. calcd for $C_9H_{10}FNS_3$: C, 43.70; H, 4.07; N, 5.66; found: C, 43.51; H, 4.19; N, 5.72%.

2,4,5-Trichlorophenyl dimethylcarbamo(dithioperoxo)thioate (4e): According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **4e** 351 mg (yield: 53 %), a white solid. M.p.: 150-154 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1H), 7.48 (s, 1H), 3.64 (s, 3H), 3.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 162.7 (d, $J_{C\text{-}F}$ = 247.0 Hz), 138.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 115.4 (d, $J_{C\text{-}F}$ = 24.0 Hz), 114.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 45.6, 41.7 ppm. Anal. calcd for $C_9H_8Cl_3FNS_3$: C, 32.49; H, 2.42; N, 4.21; found: C, 32.35; H, 42.58; N, 4.33%.

Phenyl diethylcarbamo(dithioperoxo)thioate (4f)[17]: According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **4f** 329 mg (yield: 64 %), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.56 (m, 2H), 7.34-7.25 (m, 3H), 4.10-4.04 (m, 2H), 3.88-3.82 (m, 2 H), 1.39-1.31 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2, 136.1, 128.9, 127.8, 52.0, 47.1, 13.3, 11.5 ppm. Anal. calcd for $C_{11}H_{15}NS_3$: C, 51.32; H, 5.87; N, 5.44; found: C, 51.15; H, 5.98; N, 5.35%.

4-Methylphenyl diethylcarbamo(dithioperoxo)thioate (4g)[20c]: According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **4g** 379 mg (yield: 70 %), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 2.0 Hz, 2H), 7.13 (d, *J* =2.0 Hz, 2H), 4.10-4.05 (m, 2H), 3.87-3.81 (m, 2H), 2.34 (s, 3H), 1.38-1.31 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 138.3, 132.7, 130.1, 129.7, 51.9, 47.1, 21.2, 13.2 11.5 ppm. Anal. calcd for $C_{12}H_{17}NS_3$: C, 51.30; H, 6.31; N, 5.16; found: C, 51.18; H, 6.42; N, 5.27%.

2-Fluorophenyl diethylcarbamo(dithioperoxo)thioate (4h): According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **4h** 303 mg (yield: 55 %), a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66-7.64 (m, 1H), 7.27-7.24 (m, 1H), 7.14-7.04 (m, 2H), 4.08-4.02 (m, 2H), 3.87-3.82 (m, 2H), 1.38-1.30 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 160.5 (d, $J_{C\text{-}F}$ = 245 Hz), 132.7 (d, $J_{C\text{-}F}$ = 1.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 124.5 (d, $J_{C\text{-}F}$ = 4.0 Hz), 123.0 (d, $J_{C\text{-}F}$ = 17.0 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 51.9, 47.7, 13.3, 11.4 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = -105.5 (s, 1F). Anal. calcd for $C_{11}H_{14}FNS_3$: C, 47.97; H, 5.12; N, 5.09; found: C, 47.85; H, 5.25; N, 4.98%.

2,4,5-Trichlorophenyl diethylcarbamo(dithioperoxo)thioate (4i): According to TP2, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **4i** 373 mg (yield: 52 %), a white solid. M.p.: 68-72 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.43 (s, 1H), 4.03 (s, 2H), 3.87 (s, 2H), 1.40 (s, 3H), 1.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 135.1, 131.7, 131.4, 130.9, 130.5, 129.3, 52.2, 47.5, 13.5, 11.4 ppm. Anal. calcd for $C_{11}H_{12}Cl_3NS_3$: C, 36.62; H, 3.35; N, 3.88; found: C, 36.48; H, 3.46; N, 3.96%.

Acknowledgments

The foundation support from National Natural Science Foundation of China (21302150), Hubei Provincial Science and Technology (2019CFB596), Chen-Guang program from Hubei Association for Science and Technology, Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University (KLSAOFM1810) are all greatly appreciated. K. P. thanks the support of Postgraduate Innovation Foundation from Wuhan Institute of Technology.

Keywords: dithiocarbamates • tetraalkylthiuram disulfide • selective synthesis • C-S/S-S formation

References

[1] a) Y. Wang, S. Chackalamannil, W. Chang, W. Greenlee, V. Ruperto, R. A.Duffy, R. McQuade, J. E. Lachowicz, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 891-894; b) G. Liu, J. R. Huth, E. T. Olejniczak, R. Mendoza, P. DeVries, S. Leitza, E. B. Reilly, G. F. Okasinski, S. W. Fesik, T. W. von Geldern, *J. Med. Chem.* **2001**, *44*, 1202-1210; c) G. De Martino, G. La Regina, A. Coluccia, M. C. Edler, M. C. Barbera, A. Brancale, E. Wilcox, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2004**, *47*, 6120-6123; d) M.-L. Alcaraz, S. Atkinson, P. Cornwall, A. C. Foster, D. M. Gill, L. A. Humphries, P. S. Keegan, R. Kemp, E. Merifield, R. A. Nixon, A. J. Noble, D. O'Beirne, Z. M. Patel, J. Perkins, P. Rowan, P. Sadler, J. T. Singleton, *Org. Process Res. Dev.* **2005**, *9*, 555-569; e) G. De Martino, M. C. Edler, G. La Regina, A. Coluccia, M. C. Barbera, D. Barrow, R. I. Nicholson, G. Chiosis, A. Brancale, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2006**, *49*, 947-954; f) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem*. **2014**, *57*, 2832-2842.

[2] a) C. Rafin, E. Veignie, M. Sancholle, D. Postal, C. Len, P. Villa, G. Ronco, *J. Agric. Food Chem*. **2000**, *48*, 5283-5287; b) X. Hou, Z. Ge, T. Wang, W. Guo, J. Cui, T. Cheng, C. Lai, R. Li, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4214-4219; c) G. E. Koutsoumpli, V. D. Dimaki, T. N. Thireou, E. E. Eliopoulos, N. E. Labrou, G. I. Varvounis, Y. D. Clonis, *J. Med. Chem*. **2012**, *55*, 6802-6813.

[3] C. N. Kapanda, J. Masquelier, G. Labar, G. G. Muccioli, J. H. Poupaert, D. M. Lambert, *J. Med. Chem*. **2012**, *55*, 5774-5783.

[4] R. Bessho, K. Matsubara, M. Kubota, K. Kuwakado, H. Hirota, Y. Wakazono,Y. W. Lin, A. Okuda, M. Kawai, R. Nishikomori, T. Heike, *Biochem. Pharmacol*. **1994**, *48*, 1883-1889.

[5] J. T. Wolfe, D. Ross, G. M. Cohen, *FEBS Lett.* **1994**, *352*, 58-62.

[6] a) L. Ronconi, C. Marzano, P. Zanello, M. Corsini, G. Miolo, C. Maccà, A. Trevisan, D. Fregona, *J. Med. Chem*. **2006**, *49*, 1648-1657; b) X. L. Hou, Z. M. Ge, T. M. Wang, W. Guo, J. R. Cui, T. M. Cheng, C. S. Lai, R. T. Li, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4214-4219.

[7] a) N. G. Urlyapova, A. A. Yushchenko, A. D. Daudova, V. A. Makarov, *Bull. Exp. Biol. Med*. **2007**, *143*, 327–329; b) R. Nagano, K. Shibata, T. Naito, A. Fuse, K. Asano, T. Hashizume, S. Nakagawa, *Antimicrob. Agents Chemother*. **1997**, *41*, 2278-2281.

[8] P. Morf, F. Raimondi, H.-G. Nothofer, B. Schnyder, A. Yasuda, J. M. Wessels, T. A. Jung, *Langmuir* **2006**, *22*, 658-663.

[9] B. P. Bongar, V. S. Sadavarte, L. S. Uppalla, *J. Chem. Res*. **2004**, *9*, 450-451.

[10] T. W. Greene, P. G. Wuts, *Protecting Groups in Organic Synthesis* **1999**, 484-485.

[11] D. Zhang, J. Chen, Y. Liang, H. Zhou, *Synthetic Commun*. **2005**, *35*, 521-526.

[12] A. Gucchait, N. Joardar, P. K. Parida, P. Roy, N. Mukherjee, A. Dutta, R. Yesuvadian, S. P. SinhaBabu, K. Jana, A. K. Misra, *Eur. J. Med. Chem.* 2018, *143*, 598-610.

[13] J. G. Sheppard, K. R.Frazier, P. Saralkar, M. F. Hossain, W. J. Geldenhuys, T. E. Long, *Bioorg. Med. Chem. Lett.* **2018**, *28(8),* 1298-1302.

[14] N. Azizi, F. Aryanasab, M. R. Saidi, *Org. Lett*. **2006**, *8*, 5275-5277.

[15] S. Bhadra, A. Saha, B. C. Ranu, *Green Chem*. **2008**, *10*, 1224-1230.

[16] T. Chatterjee, S. Bhadra, B. C. Ranu, *Green Chem*. **2011**, *13*,1837-1842.

[17] D. Soumya, S. Amit, *ChemistrySelect* **2018**, *3*, 42-43.

[18] C. R. Qi, T. Z. Guo, W. F. Xiong, *Synlett* **2016**, *27*, 2626-2630.

[19] a) W. Xu, M. T. Zeng, M. Liu, X. Liu, C. Z. Chang, H. Zhu, Y. S. Li, Z. B. Dong, *Chem. Lett*. **2017**, *46*, 641-643; b) W. Xu, M. T. Zeng, M. Liu, S. S. Liu, Y. S. Li, Z. B. Dong, *Synthesis* **2017**, *49*, 3084-3090; c) W. Xu, M. T. Zeng, S. S. Liu, Y. S Li, Z. B. Dong, *Tetrahedron Lett.* **2017**, *58*, 4289-4292; d) Q. Cao, H. Y. Peng, Y. Cheng, Z. B. Dong, *Synthesis* **2018**, *50*, 1527-1534; e) M. Y. Gao, W. Xu, S. B. Zhang, Y. S. Li, Z. B. Dong, *Eur. J. Org. Chem.* **2018**, *47*, 6693-6698; f) Z. B. Dong, X. Liu, C. Bolm, *Org. Lett*. **2017**, *19*, 5916-5919; g) M. T. Zeng, W. Xu, X. Liu, C. Z. Chang, H. Zhu, Z. B. Dong, *Eur. J. Org. Chem*. **2017**, 6060-6066; h) W. Xu, F. Gao, Z. B. Dong, *Eur. J. Org. Chem*. **2018**, 821-828.

[20] a) X. M. Wu, G. B. Yan, *Synlett* **2019**, *30*, 610-614. b) F. Lamar, G. August, B. Frances, W. W. *Michael. Chem-Biol. Interact.* **1978**, *23*, 215-25. c) K. Ferenc, S. Geza, S. A. Eniko, P. Janos, *Acta Chimica Academiae Scientiarum Hungaricae* **1972**, *73*, 63-72.

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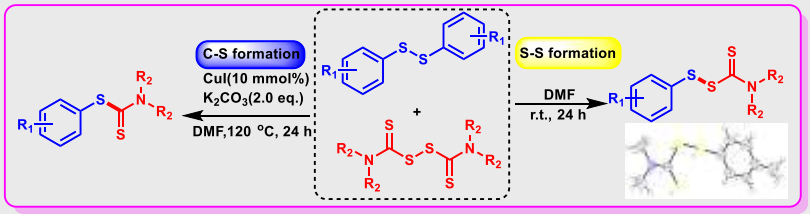

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*Kang Peng, Hui Zhu, Xing Liu, Han-Ying Peng, Jin-Quan Chen, and Zhi-Bing Dong **

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Chemo-selective C-S/S-S Formation between Diphenyl Disulfides and Tetraalkylthiuram Disulfides

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An efficient C-S/S-S formation for the chemo-selective synthesis of aryl dithiocarbamate (C-S formation) and aryl dialkylcarbamo(dithioperoxo)thioate (S-S formation) was studied. The chemo-selectivity could be controlled by modulating the reaction temperature, base, and catalyst. The transformation features simple performance, easily available starting material, high selectivity and easy performance, showing its practical synthetic value for the preparation of some potential biologically or pharmaceutically active compounds.