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Cerium ammonium nitrate-catalyzed aerobic oxidative coupling of dithiocarbamates: facile synthesis of thioureas and bis(aminothiocarbonyl) disulfides†

Tian-Tian Li,[a] Xiang-Hai Song,[a] Mei-Shuang Wang[a] and Ning Ma*[ab]

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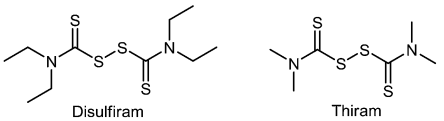
Diverse disubstituted and trisubstituted thioureas were synthesized by the condensation of dithiocarbamate TEA (or DABCO) salts and amines using cerium ammonium nitrate (CAN) as a catalyst in high yields at room temperature. It is a one-pot method and it is unnecessary to isolate isothiocyanates. This reaction probably took place through nucleophilic addition of amines to isothiocyanates, which were generated by oxidative coupling of dithiocarbamates and the following decomposition of bis(aminothiocarbonyl)disulfides. When secondary amines and CS_2 served as the reactants, bis(aminothiocarbonyl)disulfides were obtained *via* tandem nucleophilic addition/oxidative coupling reactions in moderate to excellent yields. In all the coupling reactions, the oxidant was air and CAN possibly acted as an SET catalyst.

Introduction

Thiourea is an important scaffold in medicinal chemistry. Recently, its derivatives have been reported as antitumor agents, fungicides, central nervous system (CNS) inhibitors and epigenetic modulators.[1] Thioureas have also attracted much attention due to their utilities as robust asymmetric catalysts for C–C and C–O bond formation in organic synthesis.[2] Besides, they have been widely used as building blocks for nitrogen-containing heterocycles, such as triazoles, oxadiazoles, thiadiazoles, thiazoles, pyrimidinethiones and aminohydantoins.[3] Treating amines with highly toxic thiophosgene is the traditional synthetic method toward thioureas.[4] The alternatives to thiophosgene, such as thiocarbonyldiimidazole, thiocarbonylbenzotriazoles and thiocarbamoylimidazolium salts, have been developed recently.[5] Another general route is based on the addition of amines to isothiocyanates, which are commonly prepared through reacting amines with CS_2 and the following decomposition of dithiocarbamates by various reagents, such as phosgene, phosphorus oxytrichloride, sodium hypochlorite, hydrogen peroxide, TsCl, Boc_2O, I_2, methyl acrylate and cyanuric acid.[4,6] However, isolation of isothiocyanates is commonly necessary in the above synthetic routes, which makes the overall methodology tedious and inconvenient. Recently, as the isothiocyanate equivalents, molybdenum xanthates, ethyl dithiocarbamates, and isocyanide-S have been developed to react with amines for thioureas synthesis,[7] but these routes frequently suffer from unsatisfactory yields and utility of toxic and expensive reagents. Thioureas have also been synthesized *via* one-pot direct condensation of amines and CS_2, whereas these methods were not practical for the preparation of unsymmetrical thioureas.[8] Furthermore, synthetic methods through condensation of amines and CS_2 in the presence of bases in boiling water and acetonitrile have been recently proposed.[9a,b] More recently, this transformation has been achieved under microwave irradiation.[9c] However, these methods still afforded unsymmetrical *N*,*N*′-disubstituted thioureas in poor yields. Therefore, facile synthetic approach toward thioureas, especially the unsymmetrical *N*,*N*′-disubstituted derivatives, is still of importance.

Bis(aminothiocarbonyl)disulfides have found their utilities in medicinal, agricultural and rubber chemistry in the past several decades.[10] For example, disulfiram is a medicine for treatment of chronic alcohol dependence; thiram has been involved in crop protection as a fungicide (Scheme 1). The general methods toward these compounds are treating dithiocarbamic acid salts with oxidants, such as $NaNO_2$, H_2O_2, I_2 and NaClO.[11] In these methods there remain some drawbacks, such



Scheme 1 Bis(aminothiocarbonyl)disulfides used as medicine and agrochemical.

[a]*Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, China*

[b]*Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, China. E-mail: mntju@tju.edu.cn; Fax: +86-22-27403475*

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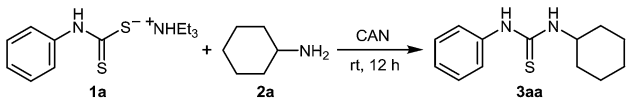
as the usage of large excess of oxidants and low yields of the products. Therefore, it is necessary to pursue more eco-friendly methods for the synthesis of disulfiram analogues.

Due to low price, low toxicity, ease of handling, experimental simplicity and solubility in a wide range of solvents, cerium ammonium nitrate (CAN) has been intensively investigated as a single-electron transfer (SET) oxidant for various chemical transformations in the past decades.[12] Recently, CAN has been frequently used as an SET or Lewis acid catalyst for the formation and cleavage of C–C, C–O, C–S and C–N bonds.[13] Herein, we wish to report that CAN serves as an SET catalyst for the synthesis of thioureas and bis(aminothiocarbonyl)disulfides from amines and CS_2, in which air acts as the oxidant.

Results and discussion

During our investigations on the reactions of dithiocarbamates,[14] we observed that CAN could promote the decomposition of dithiocarbamate salts, especially the triethylamine (TEA) salts prepared from primary amines, CS_2 and TEA. Based on this observation, the reaction of phenyldithiocarbamate TEA salt (**1a**) and cyclohexylamine has been investigated. As shown in Table 1, in the presence of 10 mol% of CAN, the reaction took place in various solvents. Acetonitrile was superior to other solvents such as water, methanol, acetone, THF, DCM and toluene (entries 1–7, Table 1). The reaction was sluggish under nitrogen atmosphere, indicating oxygen in air was necessary (entry 8, Table 1). As such, we removed the stopper several times during the reaction to perform TLC analysis and let atmospheric oxygen go into the vessel. The amount of CAN has been screened and the optimum amount was chosen as 5 mol% on the basis of the dithiocarbamate salt (entries 4, 9–13, Table 1).

Table 1 Reaction of phenyldithiocarbamate TEA salt with cyclohexylamine[a]



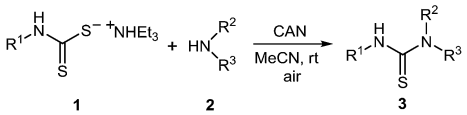
Entry	Solvent	Catalyst loading (mol%)	Yield[b] (%)
1	H_2O	10	19
2	CH_3OH	10	59
3	Acetone	10	71
4	CH_3CN	10	86
5	THF	10	82
6	DCM	10	84
7	Toluene	10	81
8	CH_3CN	10	11[c]
9	CH_3CN	0	24
10	CH_3CN	1	44
11	CH_3CN	3	77
12	CH_3CN	5	84
13	CH_3CN	15	86

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), CAN, acetonitrile 5 mL, room temperature, 12 h, under air. [b] Isolated yield. [c] Under N_2.

With the optimum conditions in hand, the scope of the reaction was investigated and the results are collected in Table 2. Various primary amines such as cyclohexylamine, *n*-octylamine, *tert*-butylamine, aniline and benzylamine reacted steadily with phenyldithiocarbamate salt **1a**, giving the corresponding thioureas **3aa–3ae** in 77–88% yields (entries 1–5, Table 2). Similarly, secondary amines such as dibutylamine, piperidine, morpholine and 1,2,3,4-tetrahydroisoquinoline could also react smoothly with **1a** to afford trisubstituted thioureas **3af–3ai** in mild to excellent yields (entries 6–9, Table 2). When the reactant was switched to 2-aminoethanol, thiourea **3aj** was isolated in 78% yield and the hydroxyl group did not take part in the condensation (entry 10, Table 2). The method was also successful for the condensation of substituted aryldithiocarbamate salts with amines. Neither electron-donating (*e.g.*, –Me, –OMe) nor weak electron-withdrawing (*e.g.*, –Cl, –Br) groups in the phenyl ring could lead to remarkable change of the yields of the corresponding thioureas (entries 11–15, Table 2). TEA salt of *m*-nitrophenyldithiocarbamic acid also reacted with *n*-octylamine to afford **3fb** in satisfactory yield (entry 16, Table 2). However, TEA and DABCO salts of *p*-nitrophenylditiocarbamic acid were hard to prepare and purify, so the corresponding *p*-nitrophenylthiourea was not obtained. Other arylthioureas such as naphthylthiourea **3gb** and pyridylthiourea **3hb** were synthesized in good yields using the corresponding dithiocarbamate salts as the substrates (entries 17 and 18, Table 2). Benzylthiourea **3ia** was similarly synthesized in excellent yield from the benzyldithiocarbamate salt **1i** (entry 19, Table 2). Satisfactorily, in the case of **1j**, the corresponding phenylaminothiourea **3ja** was produced in 81% yield (entry 20, Table 2). TEA salt of *n*-octyldithocarbamic acid (**1k**) underwent the reaction with aniline to afford thiourea **3ab** in 78% yield (entry 21, Table 2). Notably, the yield was somewhat lower than that by the condensation of phenyldithiocarbamate TEA salt with *n*-octylamine (entry 21 *vs.* entry 2, Table 2). We further attempted to synthesize bis(trifluoromethyl)phenylthioureas, but TEA salt of 3,5-bis(trifluoromethyl)phenyl dithiocarbamic acid was unstable and difficult to handle. Therfore, more stable DABCO salt was prepared and treated with various amines such as cyclohexylamine and piperidine in the presence of CAN. The corresponding thioureas were obtained in satisfactory yields (entries 22 and 23, Table 2).

Interestingly, treatment of *N*,*N*-diethyldithiocarbamate TEA salt (**1l**) with aniline in the presence of CAN afforded disulfiram (**4a**), a coupling product, instead of the corresponding thiourea (Scheme 2). Then both Et_3N and aniline were omitted, and the reactants were changed to diethylamine and CS_2. *N*,*N*-Diethyl dithiocarbamic acid was generated *in situ* by nucleophilic addition of diethylamine to CS_2, and the following dehydrogenative coupling occurred to furnish **4a** in a high yield. It is worthy to note that the reaction under open-air proceeded much more rapidly than in a sealed flask, which indicated that the coupling reaction was probably an oxidative process by atmospheric oxygen. Then the solvents, catalyst loading and reaction time were screened, and the results were collected in Table 3. The reactions in polar solvents, such as acetonitrile, dioxane, methanol, acetone, DMF and THF, underwent steadily

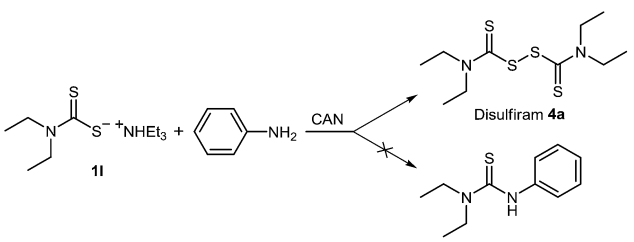
Table 2 Reactions of dithiocarbamic acid TEA salts with amines[a]



1 2 3

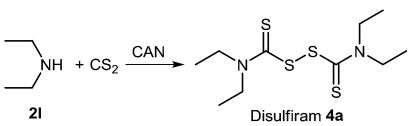
Entry	Dithiocarbamic acid salt **1**		Amine **2**		Product **3**	Mp/lit. (°C)	Yield[b] (%)
1	**1a**	R^1 = Ph	**2a**	R^2 = cyclohexyl, R^3 = H	**3aa**	143–144/144–145 (ref. 15)	86
2	**1a**		**2b**	R^2 = *n*-octyl, R^3 = H	**3ab**	49–50/52–53 (ref. 16)	88
3	**1a**		**2c**	R^2 = *t*-Bu, R^3 = H	**3ac**	121/120.5–121.5 (ref. 17)	77
4	**1a**		**2d**	R^2 = Ph, R^3 = H	**3ad**	146–147/151–152 (ref. 18)	78
5	**1a**		**2e**	R^2 = Bn, R^3 = H	**3ae**	148/153–154 (ref. 19)	79
6	**1a**		**2f**	R^2 = R^3 = *n*-Bu	**3af**	82/82 (ref. 20)	82
7	**1a**		**2g**	Piperidine	**3ag**	97/97–98 (ref. 21)	83
8	**1a**		**2h**	Morphiline	**3ah**	132–134/136–137 (ref. 22)	90
9	**1a**		**2i**	1,2,3,4-Tetrahydroisoquinoline	**3ai**	109–110/109 (ref. 23)	63
10	**1a**		**2j**	R^2 = $HOCH_2CH_2$, R^3 = H	**3aj**	136–137/137–138 (ref. 24)	78
11	**1b**	R^1 = *o*-Me-C_6H_4	**2b**		**3bb**	88–90	83
12	**1c**	R^1 = *p*-MeO-C_6H_4	**2g**		**3cg**	142–143/141–143 (ref. 25)	85
13	**1d**	R^1 = *o*-Br-C_6H_4	**2b**		**3db**	72–73	78
14	**1e**	R^1 = *p*-Cl-C_6H_4	**2a**		**3ea**	171/177–179 (ref. 26)	88
15	**1e**		**2k**	R^2 = *p*-Cl-C_6H_4, R^3 = H	**3ek**	172/171.4 (ref. 8c)	81
16	**1f**	R^1 = *m*-NO_2-C_6H_4	**2b**		**3fb**	106–108/97–99 (ref. 27)	92
17	**1g**	R^1 = 1-naphathyl	**2b**		**3gb**	71–72/71.5–72.2 (ref. 28)	80
18	**1h**	R^1 = 2-pyridyl	**2b**		**3hb**	77–78/80–82 (ref. 29)	72
19	**1i**	R^1 = Bz	**2a**		**3ia**	89–90/91–92 (ref. 30)	90
20	**1j**	R^1 = phenylamino	**2a**		**3ja**	188–190/184–185 (ref. 31)	81
21	**1k**	R^1 = *n*-octyl	**2d**		**3ab**	49–50/52–53 (ref. 16)	78
22	**1l**	R^1 = 3,5-$(CF_3)_2$-C_6H_3[c]	**2a**		**3la**	165–166/164–165 (ref. 15)	66
23	**1l**		**2g**		**3lg**	182–184/182–184 (ref. 28)	68

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CAN (5 mol%), acetonitrile (5 mL), room temperature, 12 h for using alkylamines as **2** and 24 h for arylamines, under air. [b] Isolated yield. [c] DABCO salt.



Scheme 2 The reaction of *N*,*N*-diethyldithiocarbamate TEA salt with aniline.

Table 3 CAN-catalyzed addition/coupling reaction of diethylamine and CS_2[a]



Entry	Solvent	Catalyst loading (mol%)	Time (h)	Yield[b] (%)
1	CH_3CN	0.5	3	77
2	Dioxane	0.5	3	81
3	CH_3OH	0.5	3	75
4	Acetone	0.5	6	74
5	DMF	0.5	5	69
6	THF	0.5	2	85
7	H_2O	0.5	24	20
8	THF	0.03	23	92
9	THF	0.05	9	91
10	THF	0.1	4	88
11	THF	0.2	4	87
12	THF	1	2	79
13	THF	0	24	29

[a] Reaction conditions: **2l** (4 mmol), CS_2 4.8 mmol, CAN, THF 5 mL, room temperature, under open-air. [b] Isolated yield.

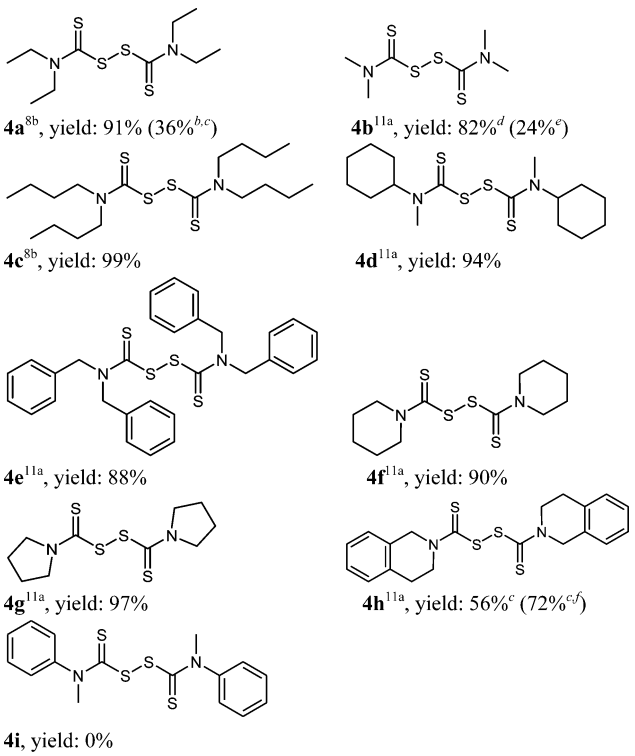
and gave **4a** in good yields (entries 1–6, Table 3). Among these solvents THF was the best. Interestingly, the reaction took place sluggishly in water, although the reaction mixture was well soluble in it (entry 7, Table 3). The amount of CAN could decrease to 0.03 mol% and the reaction was prolonged to 23 h to achieve complete conversion of **2l** (entry 8, Table 3). Increasing CAN loading made the reaction more rapid, while the yield of **4a** became lower (entry 9–12, Table 3). The catalytic activity of CAN was clear comparing to the blank run (entry 9 *vs.* entry 13, Table 3). Balancing all the above results, the optimum reaction conditions were determined as: 0.05 mol% CAN, THF as solvent, 9 h and under open-air.

Next, the scope of the substrates have been screened and the results are summarized in Table 4. Dimethylamine, dibutylamine, *N*-methylcyclohexylamine and dibenzylamine reacted smoothly with CS_2 in the presence of 0.05 mol% CAN, affording the corresponding coupling products in good to excellent yields (entries 2–5, Table 4). In the cases of cyclic secondary amines such as piperidine, tetrahydropyrrole, the reactions were also clean, producing the desired products in high yields (entries 6 and 7, Table 4). However, the reaction of tetrahydroisoquinoline and CS_2 was sluggish and the amount of CAN should be raised to 0.5 mol%. The yield of **4g** was somewhat lower due to poor solubility of the substrate and the intermediate. Water was added as co-solvent and the yield increased to 72% (entry 8, Table 4). In the case of *N*-methylaniline (**2r**), the coupling product **4i** was not obtained and **2r** was recovered (entry 9, Table 4). Notably, when dimethylamine hydrochloride was treated with CS_2 in the presence of CAN and TEA, the yield of the product **4b** was not satisfactory (entry 10, Table 4). The addition of water as co-solvent did not facilitate the reaction. Similarly, when diethyldithiocarbamate sodium salt served as the substrate instead of diethylamine and CS_2, the coupling product was isolated only in a yield of 36% (entry 11, Table 4).

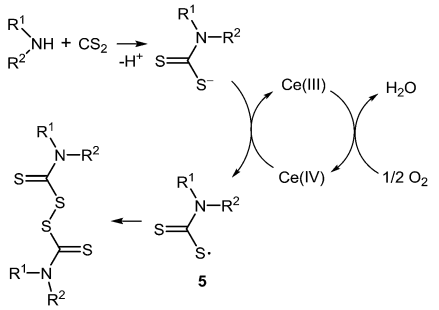
As atmospheric oxygen was needed, the coupling reaction was most likely an aerobic oxidative coupling. To illustrate the possible mechanism, further experiments were conducted. At first, the reaction of diethylamine and CS_2 in the presence of CAN was conducted under standard conditions in nitrogen atmosphere. The yield of **4a** was fairly low (19%), which supported the oxygen in air was the final oxidant. Secondly, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) was added as an inhibitor for free radical reaction. As a result, the coupling reaction was inhibited and became sluggish. The mechanisms for CAN-catalyzed aerobic oxidation reactions have been well established.[13a,32] Based on our observations and the literatures, a tentative mechanism is depicted in Scheme 3. CAN can get an electron from dithiocarbamate ion to form Ce(III) and radical **5**, from which the coupling product is generated. Meanwhile, Ce(III) is oxidized by oxygen to regenerate Ce(IV) species. Overall, CAN acts as an SET catalyst and oxygen as the oxidant.

Similar mechanism investigations were conducted on the reaction between dithiocarbamate salt **1a** and amine **2a**. Based on TLC analysis, the addition of TEMPO led to poor conversion of **1a** and formation of complicated products. Accordingly, we assume the disulfide **6a** was the initial intermediate. It was labile in the reaction system and transformed spontaneously to isothiocyanate **7a** [eqn (1), Scheme 4]. To probe this mechanism, we tried to prepared **6a** according to the procedure described in the literatures,[33] but this compound was hard to purify. As an alternative, bis(*n*-octylaminothiocarbonyl) disulfide (**6b**) was prepared. The reaction of **6b** with 2 equiv. of aniline underwent smoothly to give the corresponding thiourea **3ab** in 95% yield [eqn (2) Scheme 4]. Small amount of *n*-octyl isothiocyanate (**7b**) was also obtained, which suggested **7b** was possibly the reaction intermediate. Then we treated octyldithiocarbamate TEA salt (**1k**) with CAN in acetonitrile [eqn (3) Scheme 4]. According to TLC analysis, the reaction generated three products, two of which were probably **6b** and **7b.** Then we tried to isolate these products by column chromatography. Unfortunately, **6b** and **7b** were hard to isolate and a mixture of them was obtained as a solid. However, they could be identified by IR distinctly. As shown in Fig. 1, the IR spectrum of this isolated solid was ideally the addition of the individual spectra

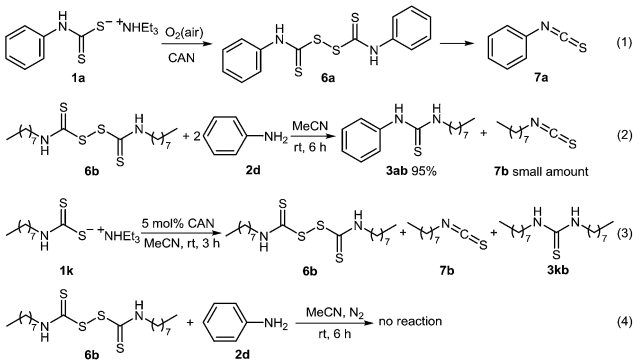
Table 4 Bis(aminothiocarbonyl)disulfides prepared from secondary amines and CS_2[a]



[a] Reaction conditions: **2** (4 mmol), CS_2 (4.8 mmol), CAN (0.05 mol%), THF (5 mL), room temperature, 9 h, under open-air. All yields are isolated yields. All spectroscopic data were in agreement with literatures.[8b,11a] [b] The starting compound was Et_2CSSNa. [c] CAN: 0.5 mol%. [d] $Me_2NH : CS_2 = 1.2 : 1$. [e] $Me_2NH_2 \cdot HCl : CS_2 : TEA = 1 : 1.2 : 1$. [f] THF/H_2O (10 : 1) as the solvent, 24 h.



Scheme 3 Plausible mechanism for the formation of bis(aminothiocarbonyl)disulfides.



Scheme 4 Mechanism studies for the formation of thioureas.

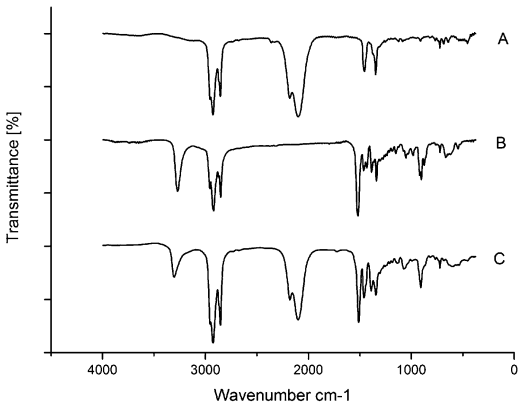
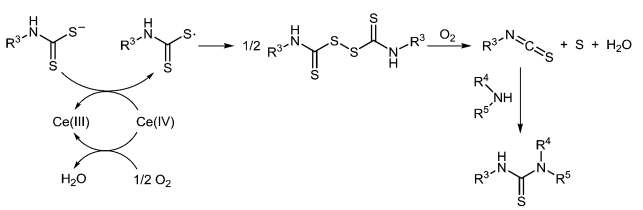


Fig. 1 IR spectra of **6b** (A), **7b** (B) and their mixture (C).

of **6b** and **7b**. Another product was also isolated and identified as *N*,*N*′-dioctylthiourea (**3kb**). It is worthy to note that **1k** was less stable than phenyldithiocarbamate TEA salts. So it partially decomposed back to octylamine (**2b**), then **3kb** was produced through nucleophilic addition of **2b** to **7b**. In the presence of aniline, the reaction of **7b** with aniline was fast, which resulted in the fast consumption of **6b** and **7b**. So under this circumstance, transformation of **1k** to **6b** was the dominant pathway and only small amount of **3kb** can generate by decomposition of **1k**. Therefore, to further avoid the decomposition of dithiocarbamate salts and decrease the amount of undesired symmetrical thioureas, more stable aryldithiocarbamate TEA salts should be employed for the synthesis of *N*-alkyl-*N*′-arylthioureas. Moreover, the reaction between **6b** and aniline did not occur in nitrogen atmosphere [eqn (4) Scheme 4]. Based on these investigations and the literature,[6a] the plausible mechanism for the formation of thioureas was proposed as depicted in Scheme 5. Aerobic oxidative coupling of dithiocarbamate leads to bis(aminothiocarbonyl)disulfide, which is sequentially oxidatively decomposed by O_2 to form isocyanate. Then nucleophilic addition of amine to isocyanate gives thiourea. Being much more stable than **6a** and **6b**, bis(aminothiocarbonyl)disulfides **4a–4h** prepared from secondary amines and CS_2 did not decompose in air to form isocyanates and the corresponding thioureas.



Scheme 5 Plausible mechanism for the formation of thioureas.

Conclusions

In summary, we demonstrated CAN-promoted synthesis of thioureas and bis(aminothiocarbonyl)disulfides, in which the oxidant was air and CAN probably served as an SET catalyst. When dithiocarbamate TEA salts, which were prepared from primary amines, CS_2 and TEA, served as the substrates, the aerobic oxidative coupling products of dithiocarbamate salts might decompose to isothiocyanates *in situ* and condense with various amines to afford the corresponding thioureas. This method is a facile one-pot process and the isothiocyanates did not need to isolate. Diverse unsymmetrical and symmetrical di- and tri-substituted thioureas could be synthesized in good to excellent yields. Furthermore, when secondary amines and CS_2 were the starting reagents, various bis(aminothiocarbonyl)disulfides were obtained by tandem nucleophilic addition/aerobic oxidative coupling in the presence of slight amount of CAN in moderate to excellent yields.

Experimental section

All commercial reagents were used as received without further purification. Column chromatography was performed over silica gel 200–300 mesh. Reactions were monitored by TLC on silica gel 60 F_{254}. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired on a Bruker AVANCE III 400 M and referenced to the internal solvents. HRMS were recorded using a Bruker MicroOTOF-QII apparatus. IR spectra were recorded in KBr on a Bruker ALPHA FT-IR instrument. Melting points were recorded on a Taike X-4 melting point apparatus and were not corrected.

General procedure for the synthesis of thioureas

Into a 25 mL flask was added acetonitrile (5 mL), dithiocarbamate TEA (or DABCO) salt **1** (ref. 34) (1 mmol), CAN (0.05 mmol) and amine **2** (1.2 mmol), then the flask was stoppered and the mixture was stirred at room temperature for 12 h (when **2** was aliphatic amine) or 24 h (when **2** was arylamine). During the reaction proceeded, the stopper was opened 3 times for about 20 s to let atmospheric oxygen go into the flask. When the reaction reached the end indicated by TLC analysis, HCl (1 M, 5 mL) and CH_2Cl_2 (10 mL) were added to quench the reaction, and the mixture was stirred until the solid dissolved. The separated aqueous solution was extracted with CH_2Cl_2 (5 mL × 2), then the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The crude product so

obtained was purified over a short column of silica gel to give the product **3**.

General procedure for the synthesis of bis(aminothiocarbonyl)disulfides

To a solution of amine (4 mmol) in 5 mL THF in a 25 mL flask was added CS_2 (4.8 mmol) followed by CAN (0.002 mmol). The mixture was stirred for 10 min with a stopper on the flask and then 9 h under open-air at room temperature. The solvent was evaporated under reduced pressure to get the crude product. Then CH_2Cl_2 (10 mL), HCl (1 M, 2 mL) was added and stirred for 10 min. The aqueous phase was separated and extracted with CH_2Cl_2 (5 mL × 2). All the CH_2Cl_2 layers were combined and dried over anhydrous $MgSO_4$. The solution was evaporated under reduced pressure to about 2 mL, and CH_3OH (5–10 mL) was added. The precipitate was filtered and dried under ambient atmosphere to get the product.

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