Novel *Self*-Condensation of Ammonium Dithiocarbamates Leading to Symmetrical Substituted Thioureas

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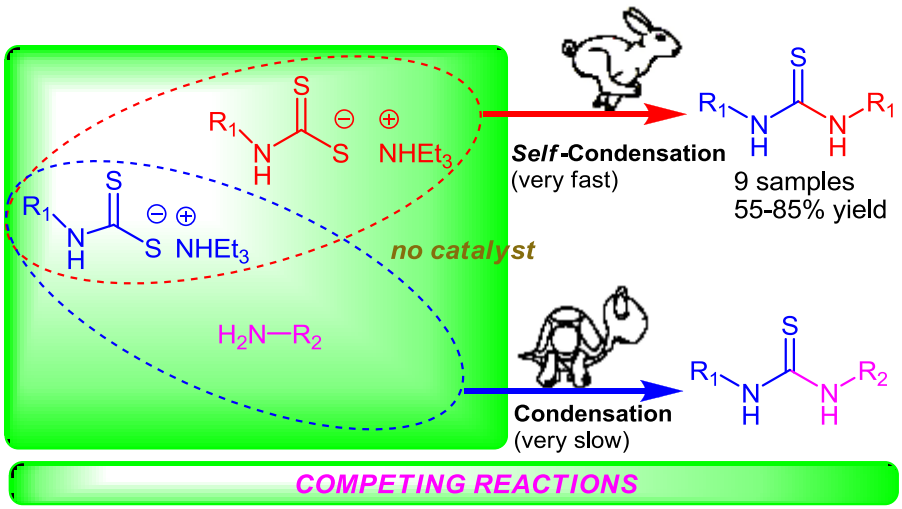
Abstract

For the first time, the formation of symmetrical substituted thiourea analogues generated by the self-condensation of trialkylammonium dithiocarbamates is reported. The reactions occurred under mild conditions. The method allows the use of amines possessing a weak nucleophilic feature in good yields. The highlight of the study is a novel self-condensation mechanism based on dithiocarbamates as a basic compound in organic chemistry.



Keywords

Self-Condensation, *N,N'*-disubstituted thiourea, ammonium dithiocarbamate, competing reactions.

Introduction

In organic synthesis, ammonium alkyl/aryl-dithiocarbamates have been widely used as an ambient nucleophile. These building blocks are capable of condensation with alkyl and acyl halides,[1–6] ketones,[7] esters,[8] aryldiazonium chlorides.[9] Besides, the dithiocarbamate derivatives could react to alkenes[10] and alkynes[8] functionalized with carbonyl group under mild conditions *via* Michael Addition. In addition, they are very useful starting materials for the synthesis of isothiocyanates by means of desulfurizing agents.[11,12]

The synthesis of thiourea from dithiocarbamate derivatives has caught the attention of chemists over several decades.[13] The published classical methods involve the preparations of thioureas from amine and isothiocyanate derivatives as key-intermediate in presence of KOH, Lac-sulfur, MCM-41-TBD, Scheme 1.[14] Recently published green and improved methods reveals that amines react with dithiocarbamic acids and their ammonium salts by sun light,[15] microwave,[16] ultra sound[17] and thermal effects[18] to afford various substituted thioureas.

With this paper we provide information about the thiourea synthesis *via* novel *self*-condensation mechanism of trialkylammonium dithiocarbamates.

Results and discussion

According to the published procedure,[5] triethylamonnium phenylditihiocarbamate (**1a**) was prepared from the reaction of aniline, carbon disulfide and triethylamine without any solvent at 0-5 ˚C, and purified by washing with diethyl ether. Then, a suspension of 10 mmol **1a** in ethyl

acetate (EtOAc) was refluxed for 15 min. At the end of the reaction time, the crude products were filtered from the cooled reaction medium, in 66% yield. ^{1}H and ^{13}C NMR data and melting point of the product clearly revealed the structure of *N*,*N*'-diphenylthiourea (**2a**).[5]

In order to propose a general reaction equation as shown Table 1, additional thiourea compounds (**2b-i**) were prepared at different patterns from various alkyl and aryl dithiocarbamates (**1b-i**),[5, 19] in moderate and good yields (55-85%).

In these reactions, notably, the transformation of ADCs to the corresponding thioureas *via* this method depends on the solubility of trialkylammonium dithiocarbamates in the warmed solvent. For instance, compound **1h** was insoluble in hot EtOAc, DMF and 1,4-dioxane. So, the self-condensation of **1h** in these solvents failed to synthesize the corresponding thiourea. However, when **1h** was warmed in DMSO to 100˚C for 15 min, the reaction product **2h** was isolated from the reaction mixture successfully, in 49%. yield Therefore some reactions were performed in DMSO and DMF as polar and inert solvents, as shown in Table 1.

The ^{1}H spectrum of **2g** showed the two NH_2 group protons at δ 7.31 ppm and two NHAr protons at 10.29 ppm. The ^{13}C atoms of **2g** were resonated by giving five signals at 180.1 ppm (C = S), and 142.8, 139.8, 126.7, 123.3 ppm (C = C). The HRMS spectrum reveals the exact chemical composition of **2g** by showing M + H signal at 387.02499.

Taking account of the nucleophilic and electrophilic characteristics of ADCs, we may suggest a three reaction pathway;

Firstly, the reactions have a *self*-condensation mechanism as shown Scheme 2a. In this mechanism, mercaptobis(alkyl/arylamino)methanethiolate might be occurred as a *key*-intermediate which offered for condensation mechanism of sodium dithiocarbamate salts with amines by Maddani *et* al.[20]

Another scenario could be outlined in Scheme 2b, perhaps, any amount of ADC in reaction mixture might lead to the corresponding isothiocyanate as key intermediate by elimination of 1 equivalent H_2S from the structure. Then, the isothiocyanate derivative reacts with the remaining ADC derivative, and yields the *N*,*N*'-disubstituted thiourea derivative.

A third possibility is that ammonium dithiocarbamate slowly decomposes back into an amine and CS_2 by thermal effect in the reaction media. This amine might react with the rest of the dithiocarbamate in the reaction mixture to form the thiourea derivative, Scheme 2c.

To reach a reliable mechanism, we investigated the intramolecular condensation of aryldithiocarbamate salts substituted with carboxylic acid group at 2-position (**3a, b**) in DMF at 100 ˚C for 15 min. When the molecular structures of the isolated products (**4a, b**) were illuminated by spectroscopic techniques, it was seen that there was no occurrence of isothiocyanate derivatives which would yield benzoxazine-4-ones, Scheme 3. Instead, the reactions have been started *via* intramolecular attack of *S*-atom to *C = O* group of carboxylic acid moiety and gave benzothiazin-4-one derivatives, in good yield (53-61%). Ccompound **4a** have been reported from same reaction earlier,[21] and its NMR data are identical with our

spectral data. Thus, it was seen that isothiocyanate does not occur as *key* intermediate in remarkable yields under these working reaction conditions and Scheme 2b is improbable.

In another respect, is Scheme 2c a possible way for the formations of the corresponding thiourea derivatives? For this question, we investigated the crude reaction products of **1f** in the presence of *p*-toluidine.

2 mmol of **1f** and 1 mmol *p*-toluidine were refluxed in dioxane for 15-20 min., Scheme 4. After evaporation of the dioxane, the crude product of competing reactions was washed with cold petroleum ether and analyzed by a ^{1}H NMR experiment. We have not observed evidence for the corresponding condensation product **5**. On the other hand, compound **2f** and *p*-toluidine were clearly detected from the spectrum of the crude product, and TLC. Amines are less reactive than ADCs for condensation to ADCs as shown Scheme 4, and the reaction pathway in Scheme 2c has is not dominant under the reaction conditions. Thus, probable *self*-condensation mechanism of ADCs has been confirmed by interpretation of the experiments including Scheme 3 and Scheme 4.

In summary, we have described an interesting and novel sample of *self*-condensation in organic chemistry. The present method for the synthesis of symmetrical substituted thioureas is different from the numerous published ones which include the condensation of amines with thiourea,[22] thiophosgene,[23] *O*-alkyl arylthiocarbamates,[24] dithiocarbamic acid or its derivatives.[14–18] This improved method corresponds to the usage of the amines bearing

electron withdrawing groups for synthesis of thioureas in good yield. Nine symmetrical *N*,*N*'-disubstituted thioureas were prepared *via* this method and three of them (**2g-i**) are new.

Experimental Section

Mp was measured on an Electro thermal 9100 apparatus and are uncorrected. Elemental analyses for C, H and N were carried out using a LECO-932 CHNS-O Elemental Analyzer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 400 spectrometer using $CDCl_3$ or DMSO−d_6 solvents. The IR spectra were recorded with ATR method using a Shimadzu 8400 and Perkin Elmer Spectrum Two Model FT-IR spectrometer. HR-MS analyses were carried out with Agilent Technologies 6224 TOF LC/MS. The compounds **1a-f**[5] and **1g**[19] were prepared according to published procedures. The Supplemental Materials contains characterization data and sample spectra for products 2a-I (Figures S 1 -- S 21)

Triethylammonium 4-carbamoylphenylcarbamodithioate (1h)

To a suspension of CS_2 (4 mmol 0.304) and 4-aminobenzamide (3 mmol, 0.408 g) in methanol (3 mL) was added triethylamine (3 mmol, 0.303 g) and the mixture was stirred at 30-40 ˚C for 20 min. During the reaction, the mixture was become a clear yellow solution, and then the product precipitated. The white precipitated solid was filtered and washed with diethyl ether.

White solid; yield: 230 mg (73%); mp 175--178°C.

Triethylammonium pyrimidin-2-ylcarbamodithioate (1i)

To solution of CS_2 (12 mmol 0.912 g) and 2-aminopyrimidine (10 mmol, 0.951 g) in DMSO (3 mL) was added triethylamine (10 mmol, 1.012 g) and the mixture was stirred at 30-40 ˚C for 1 h. The

solution contains the corresponding ammonium dithiocarbamate salt (**1i**) and this compound was used without additional purification.

General procedures for the preparation of symmetrical substituted thiourea analogs (2a-h)

A suspension of 10 mmol ADC (**1a-h**) in solvent (5 mL) given in Table 1 was warmed at the temperature which was showed in Table 1 for 15-20 min. After cooling the mixture to 5 ˚C, the precipitated product was filtered. In the event that there was no precipitate when cooling the solvent (in general for DMF or DMSO), the product was precipitated by adding 3-4 mL water. The crude products were recrystallized from corresponding solvent in Table 1.

4,4'-Thiocarbonylbis(azanediyl)dibenzenesulfonamide (2g)

White solid; yield: 1216 mg (63%); mp 230--231°C. IR (ATR): 3340, 3242, 3192, 3106 (NH), 3011 cm^{-1} (CH, Ar). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.29 (s, 2×1H, NH), 7.78–7.67 (m, 8H, Ar–H), 7.31 (s, 2×2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 180.1 (C = S), 142.8, 139.8, 126.7, 123.3 (C = C, Ar). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}N_4O_4S_3$: 387.02455; found: 387.02499. Anal. Calcd for $C_{13}H_{14}N_4O_4S_3$: C, 40.40; H, 3.65; N, 14.50; S, 24.89. Found: C, 40.54; H, 3.59; N, 14.26; S, 25.01.

4,4'-Thiocarbonylbis(azanediyl)dibenzamide (2h)

White solid; yield: 769 mg (49%); mp 283--284°C. IR (ATR): 3411 (NH), 3254, 3198 (NH_2), 1652 cm^{-1} (C = O). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 2×1H, NH), 7.31 (s, 2×2H, NH_2), 7.93–7.56 (m, 8H, Ar–H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 179.7 (C = S), 167.8 (C = O), 142.5,

130.2, 128.4, 122.6 (C = C, Ar). Anal. Calcd for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82; S, 10.20. Found: C, 57.34; H, 4.44; N, 17.73; S, 10.45.

***N,N'*-Dipyrimidin-2-ylthiourea (2i)**

The solution of **1i** in 3 mL DMSO was warmed at 100 ˚C for 15 min. After the mixture was cooled to room temperature, 2-3 mL H_2O was added. Precipitated yellow solid was filtered and then recrystallized from DMF-H_2O (1:1).

Yellow solid; yield: 638 mg (55%); mp 332--333°C. IR (ATR): 3158, 3124 (NH), 1619 cm^{-1} (C = N). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.66 (s, 1H, NH), 13.15 (s, 1H, NH), 8.30–7.30 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 188.4 (C = S), 170.9, 136.8, 136.5, 130.6, 125.7, 123.1, 116.7 (C = C, Ar). Anal. Calcd for $C_9H_8N_6S$: C, 56.54; H, 3.47; N, 36.18; S, 13.81. Found: C, 56.63; H, 3.41; N, 36.26; S, 14.03.

General procedures for the preparation of 2-thioxo-1,2-dihydro-4*H*-3,1-benzothiazin-4-one analogs (4a-b)

To solutions of anthranilic acid derivatives (10 mmol) and triethylamine (11 mmol) in 2 mL DMF were added 15 mmol CS_2, than stirred for 30 min. Meantime, triethylammonium 2-carboxyphenylcarbamodithioate derivatives were occurred in the DMF. Then, the solutions were warmed at 100 ˚C for 15 min. After cooling reaction mixtures to 5 ˚C, the products were precipitated by adding 2-3 mL water.

6-Hydroxy-2-thioxo-1*H*-benzo[*d*][1,3]thiazin-4(2*H*)-one (4b)

Orange-red solid; yield: 1280 mg (61%); mp 276--278°C. IR (ATR): 3318 (OH), 3133 (NH), 1629 (C = O), 1330 cm^{-1} (C = S). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.67 (s, 1H, NH), 10.34 (s, 1H, OH), 7.48–7.22 (m, 3H, Ar–H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 185.7 (C = S), 184.2 (C = O), 155.6, 135.6, 125.8, 121.9, 120.4, 119.2 (C = C, Ar). Anal. Calcd for $C_8H_5NO_2S_2$: C, 45.48; H, 2.39; N, 6.63; S, 30.36. Found: C, 45.23; H, 2.32; N, 6.77; S, 30.55.

Acknowledgment

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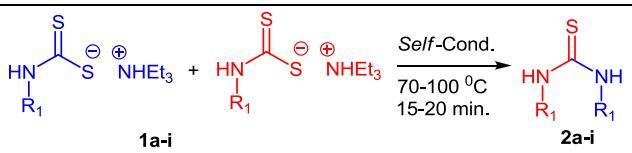
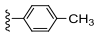
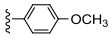
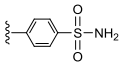
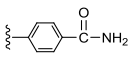
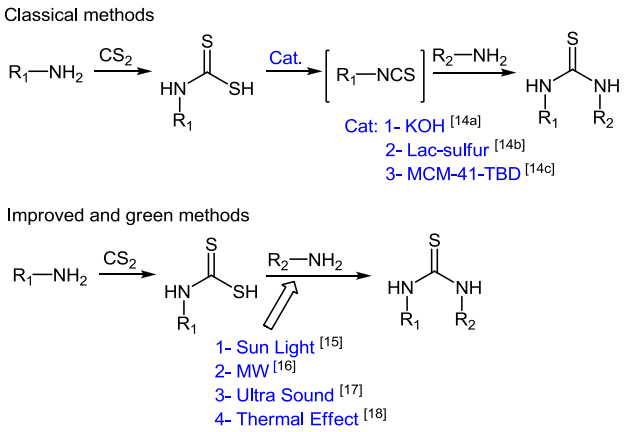
Table 1 *Self*–condensation of ADCs and the experimental data.



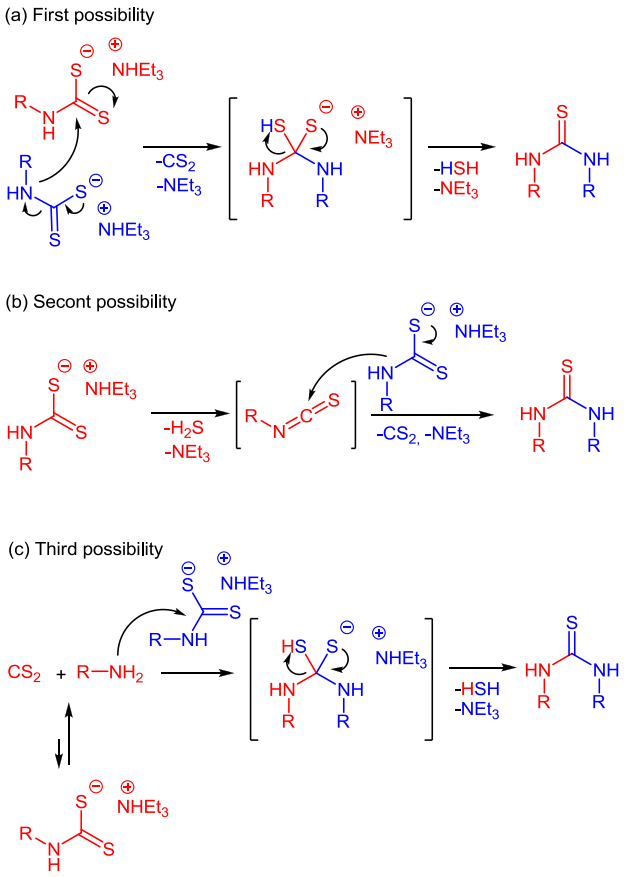
1a-i 2a-i

Entry	Product (**2a-i**)	R_1	Solvent Temp.	Recryst Yield (%)[a]	Mp(°C) Mp [Lit.]
1	**2a**		EtOAc 77 ˚C	EtOH 66	150–153 150–151[14]
2	**2b**		EtOAc 77 ˚C	Xylene 78	182–183 182–183[14]
3	**2c**		EtOAc 77 ˚C	MeOH 71	192–194 195–196[14]
4	**2d**		EtOAc 77 ˚C	MeOH 79	190–191 188–190[14]
5	**2e**		EtOAc 77 ˚C	MeOH 85	198–199 198–199[15]
6	**2f**		Dioxane 101 ˚C	EtOH 80	146–147 146–147[14]
7	**2g**		DMF 100˚C	DMF&H_2O 63	230–231
8	**2h**		DMSO 100˚C	DMF 49	283–284
9	**2i**		DMSO 100˚C	DMF&H_2O 55	332–333

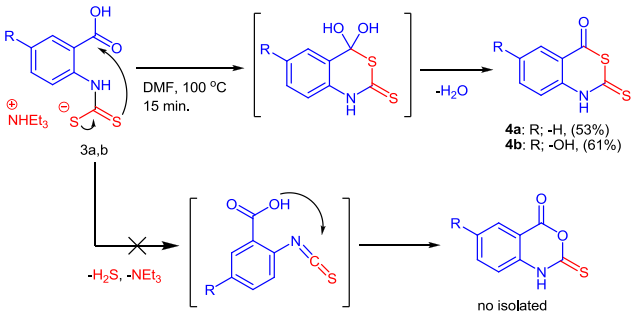
[a]Isolated yields.



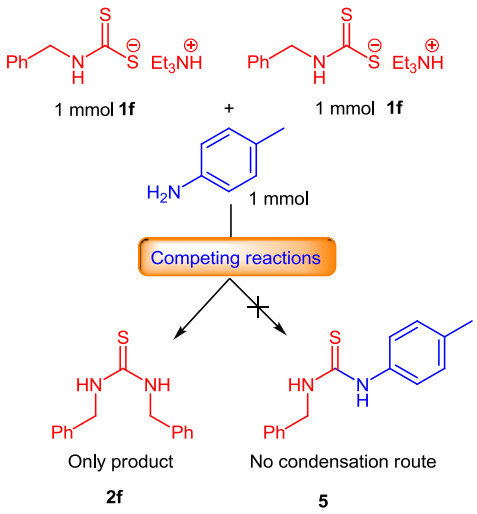
Scheme 1. Synthesis of thiourea derivatives in the literature.



Scheme 2. Probable three mechanisms of ADCs giving to symmetrical substituted thioureas.



Scheme 3. Intramolecular condensation of aryldithiocarbamate salts substituted with carboxylic acid group at 2-position.



Scheme 4. The competing reactions in one-pot reaction media at 100 ˚C for 15-20 min.