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ORIGINAL PAPER

New facile one-pot synthesis of *S*-alkyl thiolcarbamates from xanthogenate in water

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Abstract A simple and efficient one-pot synthesis was developed for the preparation of *S*-alkyl thiolcarbamates from xanthogenate without catalyst using water as a solvent. The water can be recycled after removal of the product. The significant features of this protocol are: operational simplicity, mild reaction conditions, recycling of solvent and high product yields. Starting basic alkyl xanthogenate reacts with alkyl ammonium sulfate (aryl ammonium sulfate) and hydrogen peroxide (molar ratio 1:0.55:1) in water at 40 °C for 1 h, followed by additional heating at 70–110 °C for 1–2.3 h. Good to excellent yields were achieved using ammonium sulfate in 10 % molar excess.

Keywords Amines · Catalyst-free reaction · Fungicides · Alkyl ammonium sulfate · Aryl ammonium sulfate

Introduction

Thiocarbamates, especially *S*-alkyl thiocarbamates, are mainly used in agriculture as insecticides, herbicides and fungicides. They are also used as biocides for industrial or other commercial applications and in household products. Some of them are used for vector control in public health [1–5]. In addition, they also have bactericidal, anesthetic and antiviral properties [6–9].

Due to their importance and wide application, synthesis of *S*-alkyl thiocarbamates has been widely investigated (for reviews, see [10–13]). Rearrangement of *O*-alkyl thiocarbamates to *S*-alkyl thiocarbamates was also studied. This rearrangement proceeds in the presence [14–16] or in the absence of catalyst [16]. Thermal rearrangement of *O*-allyl thiocarbamates to *S*-allyl thiocarbamates was performed at 120–150 °C [16]. Intramolecular thermal rearrangement was also investigated in the synthesis of thiolcarbamates from 2-oxo-2*H*-chromen-7-yl dimethylcarbamates using microwave irradiation in DMF. Only one product was obtained in a yield of 89 %. Starting 2-oxo-2*H*-chromen-7-yl dimethylcarbamate was obtained from 7-hydroxycoumarin, which was treated with NaH and subsequently reacted with the relevant carbamoyl chloride. The rearrangement occurs through a four-membered cyclic transition state in a concerted fashion [17]. Another intramolecular thermal rearrangement through a four-membered cyclic transition state is described. Various aryl thionobenzoates were prepared and rearranged to aryl thiolbenzoates. A four-membered cyclic transition state is formed by a nucleophilic attack of thiocarbonyl sulfur on the migrating ring [18]. It was previously shown that there is no intramolecular thermal rearrangement of *O*-alkyl thioncarbamate to *S*-alkyl thiolcarbamate without catalyst even if a reactant is heated to a boiling point for a long period of time [19].

During our previous studies of carbamate synthesis, we noticed that when the reaction mixture, which contains alkyl ammonium salt of xanthic acid, hydrogen peroxide and ammonium sulfate in excess, is heated after the disappearance of ammonium salt particles (end of oxidation

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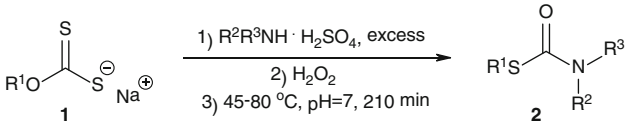
Scheme 1



and complete conversion of xanthogenate to *O*-alkyl thioncarbamate), the formation of a new compound (GC analysis). This new compound indicated the formation of *S*-alkyl thiolcarbamate. This led to the conclusion that an excess of ammonium sulfate influences the intramolecular rearrangement of thioncarbamate to thiolcarbamate.

In this article we describe one-pot synthesis of various *S*-alkyl(aryl) thiolcarbamates. Reactions take place by successive addition of reactants in aqueous media without the presence of any organic solvent. From an ecological point of view, water is the most acceptable solvent.

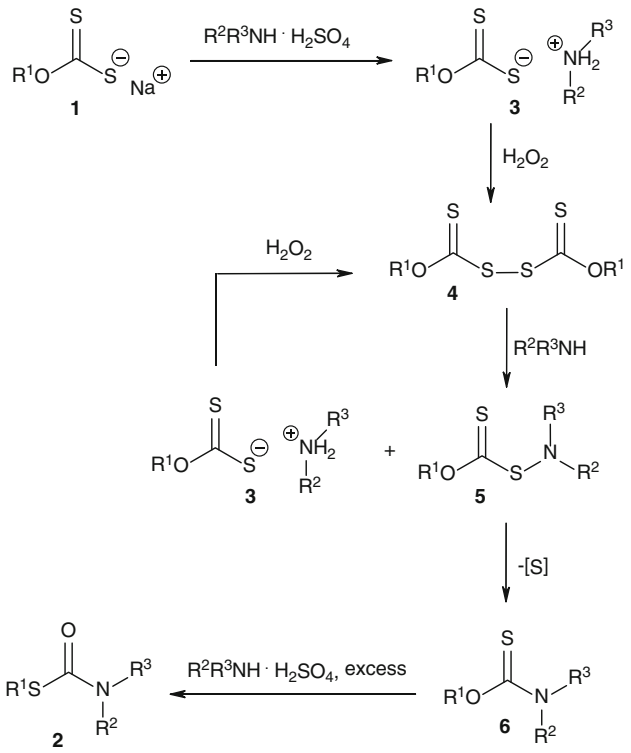
Results and discussion

A new synthetic procedure for the preparation of *N*-alkyl-(*N*-aryl-) and *N*,*N*-dialkyl-substituted *S*-alkyl thiolcarbamates **2**, starting from basic xanthogenate **1**, alkyl (aryl) ammonium sulfate (in excess) and hydrogen peroxide, is described (Scheme 1). The one-pot three-step procedure takes place without catalyst and organic solvent. This article is the continuation of our previous ones regarding the synthesis of *S*-alkyl thiolcarbamates without previous isolation of thioncarbamate from the reaction mixture [20, 21].

In the first step, when a solution of alkyl ammonium sulfate (aryl ammonium sulfate) is introduced into an aqueous solution of sodium alkyl xanthogenate **1** (equimolar amounts), a suspension of a corresponding ammonium xanthogenate **3** is formed (Scheme 2). In the second step, an oxidation using hydrogen peroxide takes place. After oxidation, the reaction mixture pH is adjusted to 7 using a 10 % solution of sulfuric acid. Disappearance of particles of ammonium xanthogenate indicates the formation of corresponding thioncarbamate **6**. By using a solution of alkyl ammonium sulfate in excess of 10 % and prolonged heating, the formation of thiolcarbamate **2** is observed (GC analysis). This clearly implies the transformation of alkyl xanthogenate to the corresponding thiolcarbamate.

Synthesized *S*-alkyl thiolcarbamate is isolated from the previously neutralized reaction mixture by simple filtration and separation of the organic phase from the aqueous. Pure product is then obtained by fractional vacuum distillation of the organic phase. The filtration cake contains sulfur, while the aqueous phase can be used again in the next synthesis. The fact that waste water from one synthesis can

Scheme 2



R^1 = Et, *i*-Pr, *i*-Bu
R^2 = Et, *n*-Pr, *i*-Pr, Ph, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$
R^3 = Et, *n*-Pr, *i*-Pr, H

be reused in another makes this procedure ecologically acceptable. In such a manner, waste water can be recycled, and after several syntheses water can be removed by evaporation to obtain sodium sulfate. This can be important for the industrial application of the procedure.

The reaction presented in Scheme 1 proceeds in three steps (Scheme 2). In the first step, alkyl ammonium salt of xanthic acid **3** is formed instantly. In the second step, oxidation by hydrogen peroxide yields dixanthogenate **4**, which is then subjected to nucleophilic attack of the amine on the S–S bond to give the corresponding sulfenamide **5**. Sulfenamide is transformed to thioncarbamate **6** by sulfur elimination. In the third step, thioncarbamate isomerizes to the corresponding thiolcarbamate **7** in the presence of excess of ammonium sulfate (Scheme 2).

The use of *p*-substituted arylamines gives solid thiolcarbamates, which can be easily separated from the reaction mixture by simple filtration. The crude products can be purified by washing with an inert solvent or recrystallizing from a non-polar solvent such as benzene, or a mixture of such solvents. *N*-alkyl-(*N*-aryl-) and *N*,*N*-dialkyl-substituted *S*-alkyl thiolcarbamates obtained in this work are summarized in Table 1.

Table 1 Synthesis of *S*-alky lthiolcarbamates

Entry	R^1	R^2	R^3	Conditions		Yield/%[c]	B.p. or m.p./°C Found (reported)
				Time/h[a]	*t*/°C[b]		
1	Et	Et	H	1.0/2.3	40/80	71	146.0–148.1/13.3[d] (116–118/32) [22]
2	Et	Et	Et	1.2/2.2	45/80	81	151.0–153.0/13.3[d] (141.5–142.0/87) [11]
3	Et	*n*-Pr	H	1.2/2.3	40/80	73	157.0–159.0/13.3[d] (120.5–120.7/20) [11]
4	Et	*n*-Pr	*n*-Pr	1.0/1.0	40/70	94	117.0–118.0/22.5[d] (137.0–138.0/40) [11]
5	Et	*i*-Pr	H	1.2/2.3	40/75	76	59.5–60.0 (60) [10]
6	Et	*i*-Pr	*i*-Pr	1.5/2.2	45/75	92	113.0–114.0/16.0[d] (113.0–114.0/28.6) [11]
7	*i*-Pr	Et	H	1.0/2.1	40/80	75	142.0–148.0/13.1[d, e] [19]
8	*i*-Pr	Et	Et	1.2/2.2	45/80	83	120.0–120.2/10.5[d, e] [19]
9	*i*-Pr	*n*-Pr	H	1.2/2.3	40/80	85	124.0–126.0/10.5[d] (97/0.66) [23, 24]
10	*i*-Pr	*n*-Pr	*n*-Pr	1.0/2.0	40/70	95	131.0–134.0/10.5[d, e] [19]
11	*i*-Pr	*i*-Pr	H	1.3/2.2	45/80	94	125.0–128.0/10.5[d, e] [19]
12	*i*-Pr	*i*-Pr	*i*-Pr	1.4/2.3	45/80	96	132.0–133.0/10.5[d, e] [19]
13	*i*-Pr	Ph	H	1.0/2.0	40/100	96	112.1–113.0 (112–113) [12]
14	*i*-Pr	4-ClC_6H_4	H	1.1/2.2	40/90	94	102.5–103.2 (102.7–103.3) [25, 26]
15	*i*-Pr	4-$MeOC_6H_4$	H	1.1/2.2	40/80	97	60.1–60.8 (60.0–60.5) [27]
16	*i*-Bu	4-MeC_6H_4	H	1.0/2.0	40/105	96	69.5–70.0 (70) [28, 29]

Reaction conditions: xanthogenate (1.0 mol), alkyl (aryl) ammonium sulfate (0.55 mol), hydrogen peroxide (1.0 mol), pH = 7

[a] First and second step reaction time/third step reaction time

[b] First and second step reaction temperature/third step reaction temperature

[c] Isolated yield

[d] Boiling point in vacuum in mbar

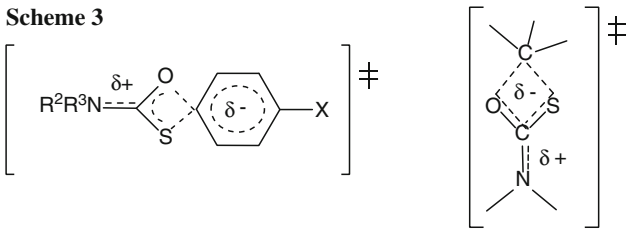
[e] IR and ^{1}H NMR spectra were found to be identical to the ones described in the reference

Good to excellent yields of the synthesized thiolcarbamate were achieved (Table 1). It should be pointed out that higher yields were achieved when secondary amines were used instead of primary ones. When arylamines were concerned, the highest yields were obtained from arylamines with electron donor groups as substituent. Therefore, the highest yields achieved were 96 and 97 % when alkylamines (diisopropylamine) and arylamines were used (4-methoxyaniline), respectively.

It was previously shown [19] that aryl thiolcarbamate synthesis can be achieved by heating of the starting aryl thioncarbamate without catalyst. On the other hand, heating of certain alkyl thioncarbamates without diethyl sulfate gives no product [19, 30, 31]. It can be seen from Table 1 that good yields were obtained when a variety of substituents were attached to nitrogen and oxygen atoms, whether *S*-ethyl- or *S*-isopropyl thiolcarbamates were concerned.

It is well known that transformation of *O*-aryl thiocarbamates to *S*-aryl thiocarbamates is an intramolecular thermal rearrangement that occurs through a four-member cyclic transition state in a concerted fashion [19, 30, 31]. This type of rearrangement is known as the Newman-Kwart rearrangement type [32]. It has been established that in order for this concerted process of C–O bond breaking and C–S bond formation in the transition state to occur, a π-system connected via oxygen to the thiocarbonyl moiety is essential. It was also established that an electron-accepting group in *para* position in the phenyl ring and an electron-donating group on nitrogen facilitate the reaction

Scheme 3



[19] (Scheme 3, left). A corresponding four-membered cyclic transition state for intramolecular rearrangement of *O*-alkyl thioncarbamates has the structure shown in Scheme 3 on the right [19]. *S*-Thiolcarbamate is then formed by the migration of the alkyl group from oxygen to sulfur.

The transition state formed during rearrangement of aryl thioncarbamates is more stable in comparison to the transition state of alkyl thioncarbamates because of the resonance stabilization of partial negative charges. If present, the electron-accepting group will additionally stabilize the transition state. Since there is no resonance stabilization in a transition state formed during alkyl thioncarbamate rearrangement, a certain degree of stabilization is achieved by the positive inductive effect of alkyl groups on nitrogen. The presence of voluminous alkyl groups such as propyl and isopropyl influence the stability of the transition state by increasing the entropy factor of free energy, thus favoring the reaction (Table 1).

Usually, the Newman-Kwart rearrangement type proceeds at high temperatures (180–300 °C) or in the presence of catalyst [19, 32]. It was also reported that the *O*-alkyl thiocarbamate to *S*-alkyl thiocarbamate rearrangement proceeds in the presence of dimethyl sulfate at 130–180 °C [30, 31] or 120–150 °C without catalyst (*O*-allyl thiocarbamate) [16]. Our procedure requires no catalyst, low reaction temperatures of 40–80 °C and a 10 % excess of ammonium sulfate.

In conclusion, this work provides a new powerful and versatile procedure for the preparation of *S*-alkyl thiolcarbamates from xanthogenate without catalyst using water as a solvent. This method is characterized by simplicity of operation, mild reaction conditions and high product yields, avoiding hazardous organic solvents, and toxic and expensive reagents. This environmentally friendly process is a suitable alternative to existing methods.

Experimental

All products were characterized by comparison of their spectral and physical data with those of known samples. ^{1}H NMR spectra were recorded on a Bruker AC 250 spectrometer at 250 MHz for ^{1}H NMR and 62.89 MHz for ^{13}C NMR spectra. The spectra were recorded at room temperature in deuterated solvent ($CDCl_3$) in 5-mm tubes. FT-IR spectra were recorded in transmission mode using a BOMEM 100 (Hartmann and Braun) spectrometer. GC analysis was performed with a Perkin-Elmer 8700 equipped with an FID detector and a column packed with 5 % OV-210 on Gas-Chrom Q [length 2 m, diameter 0.3175 cm (1/8″)]; conditions were injector temperature 250 °C, detector temperature 270 °C, column program mode: 50 °C (5 min) → 10 °C/min → 130 °C (15 min), carrier gas nitrogen (purity 99.99 %, flow 1 cm^3/min), air flow 250 cm^3/min (purity 99.99 %) and hydrogen flow 25 cm^3/min (purity 99.99 %).

Typical procedure exemplified by the preparation of S-isopropyl ethyl carbamothioate (iPrSCONHEt) using excess ammonium sulfate

In a 2,000-cm^3 three-neck round flask equipped with a condenser, dropping funnel and thermometer, 192.0 g (1.0 mol) of 82.4 % sodium isopropyl xanthogenate and 400 cm^3 of water were added with stirring. After the xanthogenate was completely dissolved, 210 cm^3 ethyl ammonium sulfate solution (0.55 mol) was added. Hydrogen peroxide (26.98 cm^3, 1.0 mol) was then added gradually for 1.2 h while the reaction temperature was maintained at 40 °C. The pH of the reaction mixture at the end of this step was 12. Then, 10 % solution of sulfuric acid was added in order to adjust the pH of the reaction mixture to 7. The reaction temperature was then increased to 75 °C and heated for an additional 2.3 h.

The reaction mixture was filtered through a Büchner funnel, separating sulfur (25.6 g, 80 % compared to the used xantogenate) from an aqueous phase that contained *S*-isopropyl ethyl carbamothioate. The filtrate was then transferred to a separation funnel, and the organic phase was separated as the upper layer. The product was obtained by vacuum distillation at 104–108 °C (660 Pa) yielding 143 g of colorless *S*-isopropyl ethyl carbamothioate (75 %). The purity of the product was determined by GC analysis (99.0 %). The water phase, which contained 0.05 mol of ethyl ammonium sulfate, could then be used for a new synthesis.

Preparation of ethyl ammonium sulfate: In a 250-cm^3 three-neck round flask equipped with a condenser, dropping funnel and thermometer, 35.4 g 70 % ethylamine (0.55 mol) and 75 cm^3 of water were added with stirring. After that, diluted sulfuric acid [28.1 g (0.275 mol) of 96 % sulfuric acid diluted with 75 cm^3 of water] was added, while keeping the reaction temperature at 30 °C, to obtain a pH of 6–7 in the reaction mixture.

Typical procedure exemplified by the preparation of S-isopropyl 4-chlorophenycarbamothioate (iPrSCONH(4-ClC$_6$H$_4$)) using excess ammonium sulfate

In a 2,000-cm^3 three-neck round flask equipped with condenser, dropping funnel and thermometer, 192.0 g of 82.4 % sodium isopropyl xanthogenate (1.0 mol) and 400 cm^3 of water were added, with stirring. After the xanthogenate had been completely dissolved, 230 cm^3 4-ClC$_6$H$_4$NH$_2$·H$_2$SO$_4$ solution (0.55 mol) was added. The ammonium solution was prepared as described before. Hydrogen peroxide (26.98 cm^3, 1.0 mol) was then added gradually for 1.1 h while the reaction temperature was maintained at 40 °C. The pH of the reaction mixture at the end of this step was 12. Then, 10 % sulfuric acid solution was added in order to adjust the pH of the reaction mixture to 7. After that, the reaction temperature was increased to 90 °C and heated for an additional 2.2 h.

The reaction mixture was cooled to room temperature and filtered through a Büchner funnel, thus separating sulfur and *S*-isopropyl 4-chlorophenycarbamothioate as a cake from an aqueous phase. The cake was washed with water, and the product was purified by crystallization from benzene. *N*-(4-chlorophenyl)-*S*-isopropyl thiolcarbamate was obtained in 94 % (215.95 g). GC purity of the product was 99.4 %, melting point 102.5–103.0 °C ([25, 26], 102.7–103.3 °C). The amount of isolated sulfur was 25.8 g (80.1 % compared to the used xanthogenate). The water phase, which contained 0.05 mol of 4-ClC$_6$H$_4$NH$_2$·H$_2$SO$_4$, can be used for a new synthesis.

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