Synthesis of dithiocarbamate by Markovnikov addition reaction in aqueous medium†

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Highly efficient, one-pot and three component reactions of amines and carbon disulfide with alkyl vinyl ethers *via* Markovnikov addition reaction were carried out in water under a mild and green procedure with excellent yields and complete regiospecificity.

Introduction

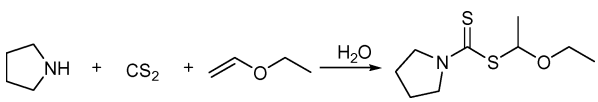
Multicomponent reactions (MCRs), which can produce a diversity of compounds, provide one of the most efficient methods for the combinatorial synthesis of structurally diverse compounds.[1] MCRs can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation that is in demand of modern synthetic design.[2] Therefore, the design of novel MCRs with green procedure has attracted great attention from research groups working in various areas such as drug discovery, organic synthesis, and material science.

Dithiocarbamates are valuable compounds due to their interesting chemistry and wide utility. These compounds have shown wide applications as pesticides, fungicides in agriculture, sulfur vulcanization in rubber manufacturing,[3–5] and radical chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerizations.[6] They have been used extensively as intermediates in organic synthesis,[7] for the protection of amino groups in peptide synthesis,[8] as linkers in solid phase organic synthesis,[9] as radical precursors[10] and recently in the synthesis of ionic liquids.[11] They have also been widely used in the synthesis of trifluoromethylamines,[12] thioureas,[13] aminobenzimidazoles,[14] isothiocyanates,[15] alkoxyamines,[16] 2-imino-1,3-dithiolane,[17] and total synthesis of (–)-aphanorphine.[18] On the other hand, dithiocarbamates are of growing interest due to their biological potencies,[19] such as antihistaminic,[20] antibacterial,[21] and anticancer activties.[22] Owing to their strong metal-binding capacity, they can also act as enzyme inhibitors, such as indoleamine 2,3-dioxygenase (IDO), which plays an important role in tumor growth.[23] For these reasons, the synthesis of dithiocarbamate derivatives with different substitution patterns at the thiol chain by a convenient and safe method has become a field of increasing interest in synthetic organic chemistry during the past few years.

Traditional methods for the synthesis of dithiocarbamates involve the use of costly and toxic reagents, such as thiophosgene, chlorothioformates, and isothiocyanates. Also, reaction of amines with carbon disulfide and alkyl halides in the presence of strong bases such as KOH and NaOH[24] or Cs_2CO_3 and TBAI[25] has been reported. However, these reactions require very toxic reagents and harmful organic solvents such as DMF, DMSO, and methanol in the presence of a catalyst. Recently the one-pot reaction of amines with carbonyl sulfide and alkyl halides, epoxide and α, β-unsaturated compounds in organic solvents or without solvent was reported by Chaturvedi *et al.* and Saidi *et al.* and their co-workers.[26] In addition, some useful reactions for the synthesis of dithiocarbamates have been reported in the literature.[27] However, most of the above described methods focused on the alkylation of dithiocarbamic acid and obtained alkyl dithiocarbamate. According to our knowledge, there are not any reports on the synthesis of dithiocarbamates by using the Markovnikov addition reaction.

Results and discussion

With the increasing interest in developing environmentally benign reactions, the atom-economic catalytic processes, or catalyst-free reactions, and the use of green solvents are ideal processes in organic chemistry. In continuation of our research toward the development of green organic chemistry by using water as the reaction medium or by performing organic transformations under solvent-free and catalyst-free conditions,[28] herein we report an efficient, novel, and environmentally benign procedure for the Markovnikov addition reaction of dithiocarbamate to alkyl vinyl ethers in aqueous medium‡ without using catalyst at room temperature (Scheme 1). The results of the present work show the desired product in excellent yield. (Table 2 and 3).



Scheme 1

Markovnikov addition reaction of dithiocarbamic acids to alkylvinyl ethers was optimized with the reaction of piperidine, CS_2, and ethyl vinyl ether as simple model substrate in different solvents and the results are summarized in Table 1. It was

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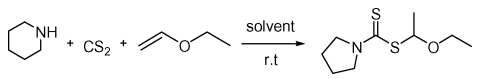
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/c004711b

‡ It is difficult to distinguish on/in water reaction in this case.[30]

Table 1 Solvent effect on the Markovnikov addition of dithiocarbamates



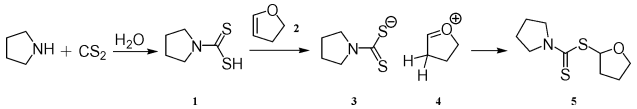
Solvent	H_2O	C_2H_5OH	CH_3OH	Diethyl ether	THF	Solvent free	$CHCl_3$	Hexane
Yield (%)[a,b]	85 (trace)[c]	86	81	38	86 (15)[c]	63	76	13

[a] Isolated yields. [b] Reaction conditions: piperidine (5 mmol), CS_2 (6 mmol), ethyl vinyl ether (6 mmol), solvent (10 mL), rt, and 16 h. [c] The reaction was carried out in the presence of 5 mmol of NaOH as base.

found that simple mixing of amine (5 mmol), carbon disulfide (6 mmol), and ethyl vinyl ether (6 mmol) gave the desired product in excellent yields in water without any catalyst at room temperature. However, the reaction gives high to excellent yields in organic solvents, but using water is the most advantageous to this method. Although the nucleophilic power of dithiocarbamate salts in basic media is more than in neutral conditions, investigations of the reaction of amines with CS_2 and then alkyl vinyl ether in basic media do not proceed well (Table 1).

After optimization of the reaction conditions, the generality of these conditions was examined by using different amines. As shown in Tables 2 and 3, different secondary amines such as pyrrolidine, piperidine, morpholine, diethylamine, and diallylamine gave excellent yields. Diisopropylamine as a hindered secondary amine gave poor results (Table 3, entry 13). Primary aliphatic amines such as benzylamine, butylamine, *sec*-butylamine, isopropylamine, and hindered primary amine such as 1-phenylethylamine undergo efficient Markovnikov addition to give only the mono adducts in excellent yields. Also amines with low solubility in water gave high to excellent yields. In addition, ethyl vinyl ether, 2,3-dihydrofuran and 2,3-dihydropyran were used as models of linear and cyclic electrophiles and gave good to excellent yields (Table 2 and 3). Dithiocarbamate derived with tryptamine with different biological activity[29] was prepared in high yields (Table 3, entry 14).

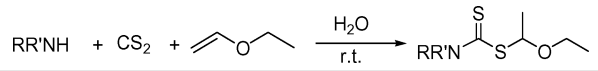
A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of the SH-acidic intermediate **1** from pyrrolidine and CS2 that can protonate the electron enriched alkene **2** to afford **4**. Subsequent nucleophilic attack of the sulfur anion **3** on **4** results in product **5**. It shows that the hydrogen of dithiocarbamic acid is necessary for progressing of the reaction and also shows why the reaction does not proceed in basic media.

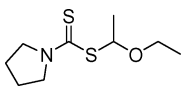
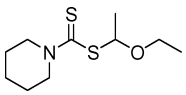
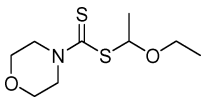
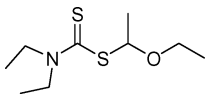
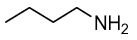
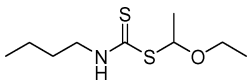
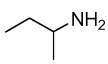
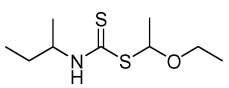
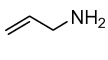
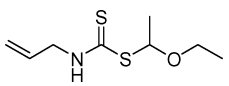
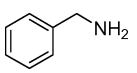
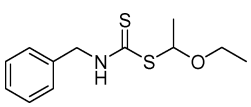
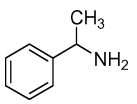
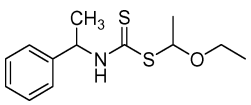
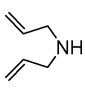
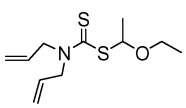
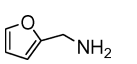
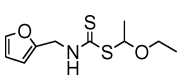


Scheme 2

Iodocyclization reaction is one the important methods for the synthesis of heterocycles. 2-Iminium-1,3-dithiolanes are a class of compounds that are safe agents for protecting crop plants from the action of herbicides. To show the efficiency of dithiocarbamate as intermediate, iodocyclization reaction of

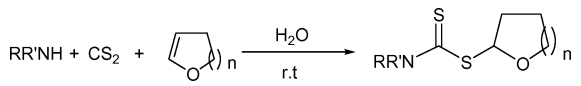
Table 2 Markovnikov addition reaction of dithiocarbamate to ethyl



Entry	Amine	Product	Yield (%)[b]
1			98
2			85
3			88
4			95 (75)[b]
5			92
6			98
7			80 (75)[b]
8			90
9			96
10			97
11			98

[a] Isolated yields. [b] The yields in parentheses refer to large scale synthesis.

Table 3 Markovnikov addition reaction of dithiocarbamate to 2,3-dihydrofuran and 2,3-dihydropyran in water



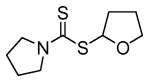
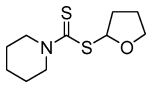
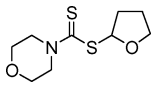
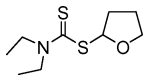
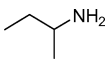
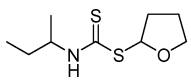
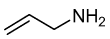
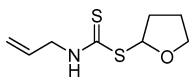
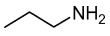
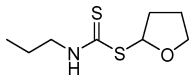
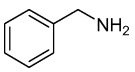
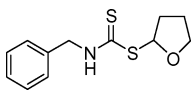
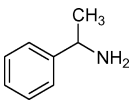
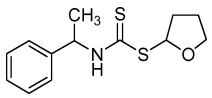
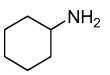
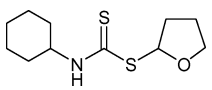
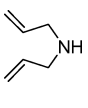
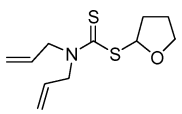
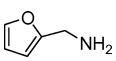
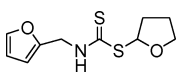
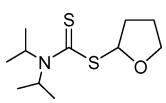
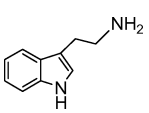
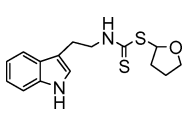
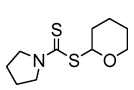
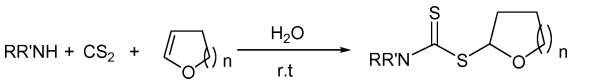
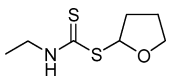
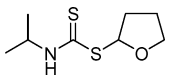
Entry	Amine	Product	Yield (%)[a]
1			78
2			71
3			82
4			65 (64)[b]
5			97
6			89
7			74
8			94 (84)[b]
9			87
10			58
11			quant. (79)[b]
12			98
13			15
14			81
15			51

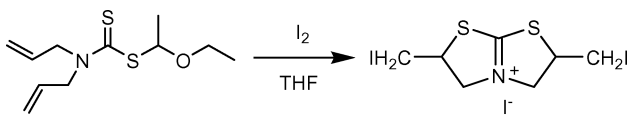
Table 3 *(Contd.)*



Entry	Amine	Product	Yield (%)[a]
16			74
17			60

[a] Isolated yields. [b] The yields in parentheses refer to large scale synthesis.

dithiocarbamate **6** proceeds to give the heterocycle **7** in good yields (Scheme 3).[17]



6 **7**

Scheme 3

Conclusion

In conclusion, we have shown a facile, highly efficient and environmentally benign procedure for one-pot synthesis of dithiocarbamates with Markovnikov addition reaction in water. This protocol avoids the use of basic and highly toxic reagents and organic solvents, such as DMF or DMSO, and catalysts by playing the dual role of water as a solvent and a promoter. In addition, the reaction shows complete regiospecificity for Markovnikov adducts. Furthermore, other advantageous of this procedure including excellent yields, clean reaction conditions, catalyst-free, and simple experimental procedures make it a useful and attractive strategy in MCRs in combinational chemistry. Although extraction of the products with organic solvents from aqueous medium is a disadvantage of the reactions in water,[30] in our process the work-up is easy for large scales; simply decanting and washing the organic phase with water and direct evaporation of unreacted material (carbon disulfide and alkyl vinyl ether) gives the products with excellent purity without need to column chromatography in most of the cases.

Experimental

General Procedure for the Markovnikov addition reaction

To a mixture of an amine (5 mmol) and carbon disulfide (6 mmol) in water (10 mL) was added an electrophile (6 mmol). The reaction mixture was stirred vigorously at room temperature for 16 h. Then, the products were extracted with ethyl acetate (2 × 20) and the combined organic layers were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the products with high purity in most of

the cases. If needed, the products were purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether; 2/8). The products were characterized by their IR, ^{1}H and ^{13}C NMR spectra and CHN analyses.

Typical procedure for large scale synthesis of 1-ethoxyethyldiethylcarbamodithioate

In a 500 mL round bottom flask, diethyl amine (35 g, 50 mL, 0.48 mol), water (300 mL) and CS_2 (41.8 g, 33.2 mL, 0.55 mol) were added respectively. To this vigorously stirred reaction mixture, ethyl vinyl ether (39.6, 52.5 mL, 0.55 mol) was added slowly and stirred at room temperature for 16 h. In completion, the organic phase was decanted and washed three times with water. Then, the organic phase was evaporated under reduce pressure to remove excess unreacted materials (CS_2: b.p. 46.3 °C; ethyl vinyl ether: b.p. 34–36 °C) to prepare 1-ethoxyethyldiethylcarbamodithioate with excellent purity and yields (82.7 g, 78%).

Experimental procedure for synthesis of iodocyclization product 7

To a stirred solution of α-(ethoxyethyl)-diallyl dithiocarbamate **6** (1 mmol) in THF (5 mL) was added I_2 (2.5 mmol) and the reaction mixture stirred for 48 h at room temperature. The resulting yellow precipitate was filtered off and washed with THF to give the product **7** in 65% yields.

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