Regiospecific Synthesis of Dithiocarbamates via a Markovnikov Addition Reaction

Azim Ziyaei Halimehjani,* Hamed Pasha Zanussi, Mohammad Amin Ranjbari

Faculty of Chemistry, Kharazmi University, 49 Mofateh St., Tehran, Iran
Fax +98(21)88820992; E-mail: ziyaei@khu.ac.ir

Received: 21.01.2013; Accepted after revision: 06.03.2013

Abstract: A simple, efficient, and regiospecific method for the synthesis of dithiocarbamates by the one-pot, three-component Markovnikov addition reaction of an amine, carbon disulfide, and *N*-vinylpyrrolidone is described.

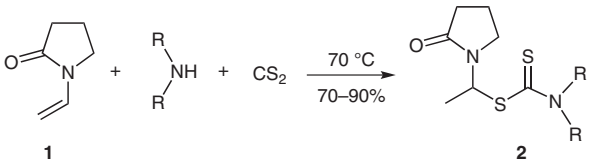
Key words: dithiocarbamates, Markovnikov addition, regiospecificity, multicomponent reactions

Development of strategically important processes which are environmentally benign with efficient and green procedures, leading to the formation of new, useful compounds via simple methodology and workup with low toxicity materials, is currently receiving considerable attention.[1] Compared to reactions with solvent, solvent-free reactions result in reduced pollution and decreased handling and labor costs due to simplification of experimental procedures and workup techniques. These factors would be especially important during industrial production and are in agreement with the goals of green chemistry.[2]

Multicomponent reactions (MCRs) are flexible reactions for the rapid generation of complex molecules, often with biologically relevant scaffold structures. Therefore, the design of novel MCRs with green procedures has attracted great attention from research groups working in various areas, such as drug discovery, organic synthesis, and materials science.[3]

In recent years, dithiocarbamates (DTCs) and their synthesis with a green procedure have received great attention, because of their indisputable applications. These synthetic compounds play important roles in both research and industry. For example, dithiocarbamates have been used in agriculture as pesticides and fungicides, for sulfur vulcanization in rubber manufacturing,[4,5] and as radical chain-transfer agents in reversible addition–fragmentation chain-transfer (RAFT) polymerizations.[6] They have also been extensively used as intermediates in organic synthesis,[7] for the protection of amino groups in peptide synthesis,[8] in the synthesis of thioureas,[9] isothiocyanates,[10] 2-imino-1,3-dithiolane,[11] cynamides,[12] and ionic liquids,[13] and in amide bond formation.[14] They show wide biological activities, such as antitumor, anticancer, and antibacterial activities.[15] They are also efficient ligands in surface science and nanomaterials chemistry.[16] 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. The Markovnikov addition reaction is a powerful tool for the formation of a carbon–heteroatom bond. We have previously reported a facile, highly efficient, and environmentally benign procedure for the one-pot synthesis of dithiocarbamates with the Markovnikov addition reaction in water using alkyl vinyl ethers as the electrophile.[17] It is worthwhile noting that electron-rich alkenes, such as enamides, which have proven to be useful reagents that are widely utilized in organic synthesis,[18] have seldom been considered as convenient candidates for alkylation, probably due to their weak electrophilicity. Dithiocarbamic acids are good nucleophiles and react with different electrophiles, including alkyl halides, epoxides, and α,β-unsaturated carbonyl compounds;[19] however, to the best of our knowledge, there are no reports on the synthesis of dithiocarbamates using an enamide as electrophile.

With the increasing interest in the development of environmentally benign reactions, atom-economic processes, and catalyst-free conditions, MCRs are ideal processes in organic chemistry. With these goals in mind and in continuation of our research toward the synthesis of novel dithiocarbamates, herein we report an efficient, novel, and environmentally benign procedure for the synthesis of dithiocarbamates via the Markovnikov addition reaction by simple mixing of an amine, carbon disulfide, and *N*-vinylpyrrolidone (**1**), with excellent yields of the products **2** (Scheme 1).

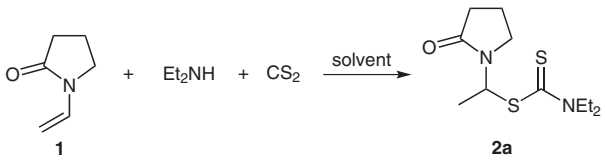


Scheme 1

We began our investigation with the one-pot, three-component reaction of diethyl amine, carbon disulfide, and *N*-vinylpyrrolidone (NVP, **1**) in various organic solvents at room temperature; the product was obtained in poor yield. Increasing the temperature to 50–70 °C resulted in increased yields in most solvents (Table 1). The best yield was obtained in *N*,*N*-dimethylformamide and the reaction also gave a high yield in an ionic liquid medium (1-butyl-

SYNTHESIS 2013, 45, 1483–1488
Advanced online publication: 09.04.2013
DOI: 10.1055/s-0032-1318504; Art ID: SS-2013-N0061-OP

Table 1 Effect of Solvent on the Markovnikov Addition Reaction of Dithiocarbamic Acid to NVP (**1**)[a]



1 **2a**

Solvent	H_2O[b]	MeCN[b]	Acetone[b]	MeOH[b]	DMF[c]	THF[b]	IL[c,d]	Neat[c]
Yield[e] (%)	n.r.[f]	45	66	46	75	73	70	90

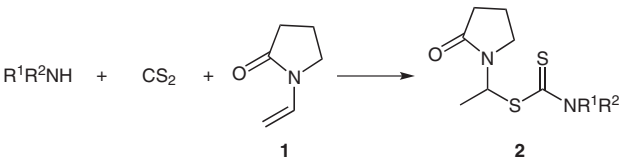
[a] Reaction conditions: Et_2NH (4 mmol), CS_2 (5 mmol), NVP (3 mmol).
[b] Reflux conditions.
[c] The reaction was carried out at 70 °C.
[d] IL = 1-butyl-3-methylimidazolium chloride.
[e] Isolated yields.
[f] No reaction.

3-methylimidazolium chloride). It was not possible to carry out the reaction in water. Surprisingly, we found that an excellent yield of product was obtained when the starting materials were mixed without any organic solvent. Thus, by simple mixing of the amine (4 mmol), carbon disulfide (5 mmol), and NVP (3 mmol), the desired product was obtained in excellent yield, without using any catalyst, at 70 °C. The purification procedure for this reaction is very simple: the product precipitated upon treatment of the reaction mixture with water, and can be collected by filtration. The reaction is regiospecific toward the Markovnikov adduct.

After optimization of the reaction conditions, the generality of these conditions was examined by using different amines. As shown in Table 2, primary aliphatic amines such as propylamine, allylamine, cyclohexylamine, benzylamine, furfurylamine, and 1-phenylethylamine were used in this process, with high yields (entries 1–6). Different secondary amines such as dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine, and azepane gave excellent yields (entries 7–12). Highly hindered amines such as *tert*-butylamine and 1-aminoadamantane did not give any addition product; also, aromatic amines are not suitable for this reaction. We have only used NVP as the electrophile in this reaction; other enamides were not examined.

It has been shown that the fungicidal activity of a compound can be increased by increasing the number of dithiocarbamate moieties in the structure.[20] For this purpose, bis(dithiocarbamates) were synthesized with the one-pot, three-component cascade Markovnikov addition reaction using diamines such as piperazine, ethylenediamine, and 1,3-benzenedimethanamine, carbon disulfide, and NVP, in good to high yields (Table 3, entries 1–3).

Table 2 Diversity in the Markovnikov Addition Reaction of Dithiocarbamic Acids to NVP (**1**)



1 **2**

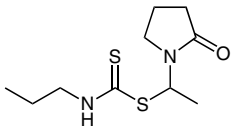
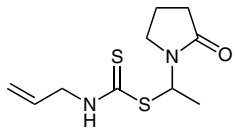
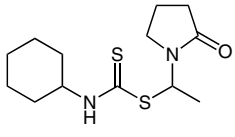
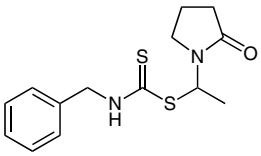
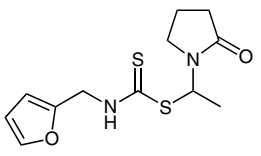
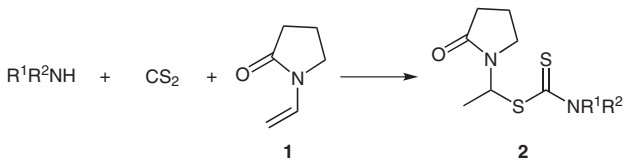
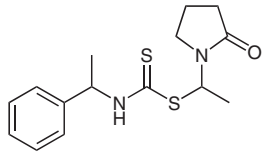
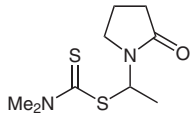
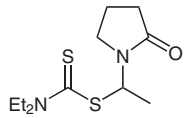
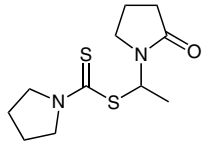
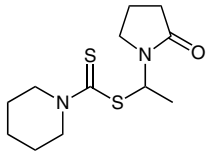
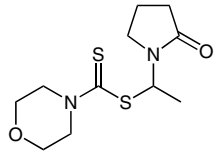
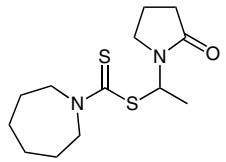
Entry	Product	Yield[a] (%)
1	 **2a**	82
2	 **2b**	73
3	 **2c**	80
4	 **2d**	83
5	 **2e**	85

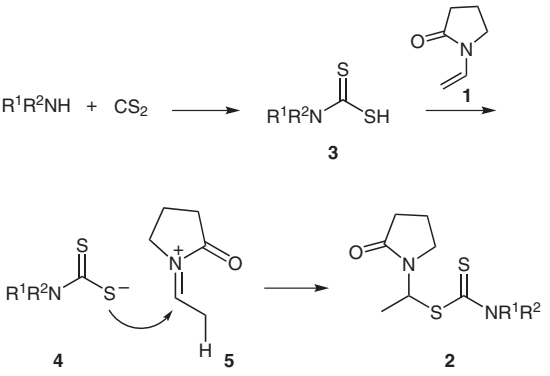
Table 2 Diversity in the Markovnikov Addition Reaction of Dithiocarbamic Acids to NVP (**1**) (continued)



Entry	Product	Yield[a] (%)
6	 **2f**	80
7	 **2g**	70
8	 **2h**	90
9	 **2i**	87
10	 **2j**	90
11	 **2k**	88
12	 **2l**	85

[a] Isolated yields.

The proposed mechanism for the formation of the Markovnikov adducts is given in Scheme 2. Reaction of an amine with carbon disulfide gives the dithiocarbamic acid **3** which can protonate the electron-enriched alkene NVP (**1**) to afford **5**. Subsequent nucleophilic attack of the dithiocarbamate anion **4** on **5** results in the product **2**. This proposal shows that the hydrogen of the dithiocarbamic acid is necessary for the reaction to progress and also explains why the reaction does not proceed in the case of N^1,N^1-dimethylethane-1,2-diamine (Table 3, entry 4) and in basic media (the reaction is not possible in the presence of NaOH or Et_3N as base).



Scheme 2

In conclusion, we have described a simple and mild protocol for the synthesis of a new class of dithiocarbamates by the one-pot, three-component Markovnikov addition reaction of an amine, carbon disulfide, and *N*-vinylpyrrolidone. The reaction can be carried out in the absence of any solvent and catalyst. Other advantages of this procedure are the high to excellent yields, regiospecificity toward the Markovnikov adduct, and simple workup. The synthesized compounds are similar to those reported by Sathiyanarayanan and co-workers,[21] and they may have biological activities.

Melting points were determined with a Branstead Electrothermal 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT RX1 spectrophotometer over the range 400–4000 cm^{-1}. ^1H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard on a Bruker AMX 300 MHz instrument. Elemental analyses were conducted with a Perkin-Elmer 2004 (II) CHN analyzer.

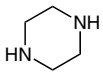
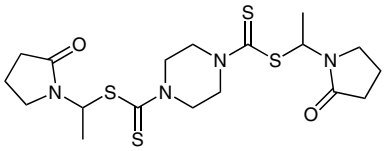
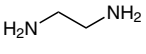
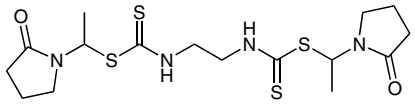
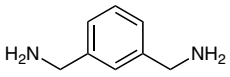
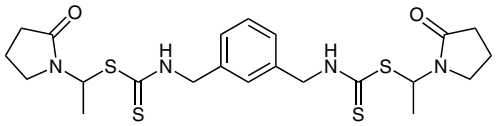
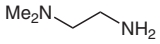
Dithiocarbamates via Markovnikov Addition; General Procedure

To a mixture of 1-vinylpyrrolidin-2-one (0.32 mL, 3.0 mmol) and CS_2 (0.18 mL, 5.0 mmol), an amine (4.0 mmol) was added. The reaction mixture was stirred vigorously at 70 °C for 6 h, then was quenched with H_2O (10 mL). The precipitated product was collected by filtration and washed several times with H_2O. In most cases, pure product was obtained. Further purification was by recrystallization (EtOH). In the case of diamines (3 mmol), CS_2 (0.42 mL, 7 mmol) and 1-vinylpyrrolidin-2-one (0.64 mL, 6 mmol) were used. It should be noted that in large-scale syntheses, the excess CS_2 was removed by simple distillation from the reaction mixture. The products were characterized by their IR, ^1H NMR, and ^{13}C NMR spectra, and CHN analyses.

1-(2-Oxopyrrolidin-1-yl)ethyl Propylcarbamodithioate (2a)

Yield: 0.605 g (82%); yellow solid; mp 76–78 °C.

Table 3 Synthesis of Bis(dithiocarbamates) via the Markovnikov Addition Reaction

Entry	Diamine	Product	Yield[a] (%)
1		 **2m**	79
2		 **2n**	35
3		 **2o**	70
4		–	n.r.[b]

[a] Isolated yields.
[b] No reaction.

IR (KBr): 3185, 2961, 1662, 1552, 1420, 951, 890 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3 H), 1.50 (d, *J* = 7.2 Hz, 3 H), 1.74 (m, 2 H), 2.13 (m, 2 H), 2.49 (m, 2 H), 3.44–3.67 (m, 4 H), 5.92 (q, *J* = 7.2 Hz, 1 H), 9.46 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 17.4, 17.8, 21.1, 31.0, 42.0, 49.1, 53.5, 176.4, 192.2.

Anal. Calcd for $C_{10}H_{18}N_2OS_2$: C, 48.75; H, 7.36; N, 11.37. Found: C, 48.75; H, 7.44; N, 11.36.

1-(2-Oxopyrrolidin-1-yl)ethyl Allylcarbamodithioate (2b)
Yield: 0.534 g (73%); yellow solid; mp 73–76 °C.

IR (KBr): 3170, 2960, 1660, 1552, 1204, 1057, 924 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.1 Hz, 3 H), 2.15 (m, 2 H), 2.49 (m, 2 H), 3.46 (m, 1 H), 3.60 (m, 1 H), 4.35 (m, 2 H), 5.29 (m, 2 H), 5.94 (m, 2 H), 9.58 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 17.9, 31.0, 42.1, 49.6, 53.7, 118.3, 131.5, 176.5, 192.7.

Anal. Calcd for $C_{10}H_{16}N_2OS_2$: C, 49.15; H, 6.60; N, 11.46. Found: C, 49.26; H, 6.73; N, 11.44.

1-(2-Oxopyrrolidin-1-yl)ethyl Cyclohexylcarbamodithioate (2c)
Yield: 0.686 g (80%); white solid; mp 104–107 °C.

IR (KBr): 3252, 2921, 1667, 1530, 1392, 1088, 928 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.42 (m, 5 H), 1.52 (d, *J* = 7.2 Hz, 3 H), 1.65–1.83 (m, 3 H), 2.11–2.16 (m, 4 H), 2.46–2.53 (m, 2 H), 3.44 (m, 1 H), 3.62 (m, 1 H), 4.38 (m, 1 H), 5.89 (q, *J* = 7.0 Hz, 1 H), 9.21 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 17.8, 24.9, 25.0, 25.2, 31.1, 31.2, 31.5, 42.0, 53.3, 56.2, 176.1, 190.7.

Anal. Calcd for $C_{13}H_{22}N_2OS_2$: C, 54.51; H, 7.74; N, 9.78. Found: C, 54.53; H, 7.92; N, 9.75.

1-(2-Oxopyrrolidin-1-yl)ethyl Benzylcarbamodithioate (2d)
Yield: 0.732 g (83%); white solid; mp 93–96 °C.

IR (KBr): 3158, 2952, 1654, 1536, 1284, 1094, 937 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.1 Hz, 3 H), 2.06 (m, 2 H), 2.25 (m, 1 H), 2.43 (m, 1 H), 3.43 (m, 1 H), 3.57 (m, 1 H), 4.94 (m, 2 H), 5.90 (q, *J* = 7.2 Hz, 1 H), 7.37 (m, 5 H), 9.81 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 17.7, 30.8, 42.0, 50.2, 53.6, 127.6, 128.3, 128.4, 136.2, 176.5, 192.8.

Anal. Calcd for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16; N, 9.51. Found: C, 57.24; H, 6.18; N, 9.60.

1-(2-Oxopyrrolidin-1-yl)ethyl Furan-2-ylmethylcarbamodithioate (2e)
Yield: 0.724 g (85%); yellow solid; mp 84–86 °C.

IR (KBr): 3136, 2971, 1664, 1552, 1205, 1083, 924, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.2 Hz, 3 H), 2.10 (m, 2 H), 2.44 (m, 2 H), 3.43 (m, 1 H), 3.57 (m, 1 H), 4.82–5.00 (m, 2 H), 5.92 (q, *J* = 7.2 Hz, 1 H), 6.37–6.38 (m, 2 H), 7.42 (s, 1 H), 9.78 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 17.8, 30.8, 42.1, 43.3, 53.7, 109.0, 110.4, 142.4, 149.1, 176.6, 193.1.

Anal. Calcd for $C_{12}H_{16}N_2O_2S_2$: C, 50.68; H, 5.67; N, 9.85. Found: C, 50.79; H, 5.60; N, 9.88.

1-(2-Oxopyrrolidin-1-yl)ethyl 1-Phenylethylcarbamodithioate (2f)
Yield: 0.740 g (80%); yellow solid; mp 127–130 °C.

IR (KBr): 3286, 2988, 1669, 1654, 1547, 1281, 1086, 966, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.0 Hz, 3 H), 1.71 (d, *J* = 7.0 Hz, 3 H), 2.00–2.18 (m, 3 H), 2.44 (m, 1 H), 3.40 (m, 1 H), 3.55 (m, 1 H), 5.82 (m, 1 H), 5.99 (m, 1 H), 7.25–7.44 (m, 5 H), 9.53 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 20.6, 30.9, 41.9, 53.5, 54.0, 55.6, 125.5, 126.8, 127.4, 128.3, 176.3, 191.3.

Anal. Calcd for $C_{15}H_{20}N_2OS_2$: C, 58.41; H, 6.54; N, 9.08. Found: C, 58.72; H, 6.36; N, 9.27.

1-(2-Oxopyrrolidin-1-yl)ethyl Dimethylcarbamodithioate (2g)
Yield: 0.487 g (70%); white solid; mp 118–120 °C.

IR (KBr): 2934, 1686, 1507, 1262, 1050, 980 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (d, *J* = 7.0 Hz, 3 H), 2.05 (m, 2 H), 2.40 (m, 2 H), 3.35–3.62 (m, 8 H), 6.08 (q, *J* = 7.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 19.8, 31.2, 41.5, 44.9, 45.8, 61.2, 174.8, 194.7.

Anal. Calcd for $C_9H_{16}N_2OS_2$: C, 46.52; H, 6.94; N, 12.06. Found: C, 46.67; H, 7.08; N, 11.85.

1-(2-Oxopyrrolidin-1-yl)ethyl Diethylcarbamodithioate (2h)
Yield: 0.702 g (90%); white solid; mp 76–80 °C.

IR (KBr): 2970, 1701, 1494, 1197, 1044, 912 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (m, 6 H), 1.76 (d, *J* = 7.0 Hz, 3 H), 2.05 (m, 2 H), 2.42 (m, 2 H), 3.46 (m, 1 H), 3.60–3.74 (m, 3 H), 3.99 (m, 2 H), 6.13 (q, *J* = 7.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 12.5, 18.2, 20.0, 31.3, 45.9, 46.8, 49.0, 60.8, 174.8, 193.2.

Anal. Calcd for $C_{11}H_{20}N_2OS_2$: C, 50.73; H, 7.74; N, 10.76. Found: C, 50.95; H, 8.07; N, 10.73.

1-(2-Oxopyrrolidin-1-yl)ethyl Pyrrolidine-1-carbodithioate (2i)
Yield: 0.673 g (87%); white solid; mp 106–109 °C.

IR (KBr): 2949, 1696, 1443, 1250, 1159, 1000, 949 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (d, *J* = 7.0 Hz, 3 H), 1.92–2.06 (m, 6 H), 2.36 (m, 2 H), 3.54–3.59 (m, 4 H), 3.87 (m, 2 H), 6.10 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 19.9, 24.0, 25.8, 31.1, 45.7, 50.5, 54.5, 59.9, 174.6, 190.2.

Anal. Calcd for $C_{11}H_{18}N_2OS_2$: C, 51.13; H, 7.02; N, 10.84. Found: C, 50.98; H, 7.02; N, 10.82.

1-(2-Oxopyrrolidin-1-yl)ethyl Piperidine-1-carbodithioate (2j)
Yield: 0.734 g (90%); white solid; mp 57–60 °C.

IR (KBr): 2952, 1694, 1481, 1242, 978 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71–1.75 (m, 9 H), 2.04 (m, 2 H), 2.40 (m, 2 H), 3.42–3.64 (m, 2 H), 3.86 (br s, 2 H), 4.29 (br s, 2 H), 6.14 (q, *J* = 7.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 19.9, 24.1, 25.3, 25.9, 31.3, 45.8, 51.4, 52.3, 60.7, 174.8, 193.0.

Anal. Calcd for $C_{12}H_{20}N_2OS_2$: C, 52.90; H, 7.40; N, 10.28. Found: C, 52.71; H, 7.40; N, 10.40.

1-(2-Oxopyrrolidin-1-yl)ethyl Morpholine-4-carbodithioate (2k)
Yield: 0.723 g (88%); white solid; mp 108–110 °C.

IR (KBr): 2924, 1695, 1458, 1267, 1112, 994 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (d, *J* = 7.01 Hz, 3 H), 1.98–2.06 (m, 2 H), 2.33–2.38 (m, 2 H), 3.37–3.71 (m, 6 H), 3.87 (br s, 2 H), 4.25 (br s, 2 H), 6.03–6.16 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 19.7, 31.0, 45.4, 50.4 (2 C), 60.4, 65.9 (2 C), 174.7, 194.7.

Anal. Calcd for $C_{11}H_{18}N_2O_2S_2$: C, 48.15; H, 6.61; N, 10.21. Found: C, 48.06; H, 6.93; N, 9.87.

1-(2-Oxopyrrolidin-1-yl)ethyl Azepane-1-carbodithioate (2l)
Yield: 0.729 g (85%); yellow solid; mp 69–71 °C.

IR (KBr): 2919, 1698, 1416, 1260, 1169, 1044, 943 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (m, 4 H), 1.65–1.78 (m, 7 H), 1.97 (m, 2 H), 2.33 (m, 2 H), 3.37–3.53 (m, 2 H), 3.78 (m, 2 H), 4.06–4.15 (m, 2 H), 6.08 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 19.7, 25.8, 26.2, 26.3, 27.1, 31.0, 45.4, 52.6, 54.9, 60.2, 174.5, 193.5.

Anal. Calcd for $C_{13}H_{22}N_2OS_2$: C, 54.51; H, 7.74; N, 9.78. Found: C, 54.83; H, 8.20; N, 9.56.

Bis[1-(2-oxopyrrolidin-1-yl)ethyl] Piperazine-1,4-dicarbodithioate (2m)
Yield: 1.09 g (79%); yellow solid; mp 162–165 °C.

IR (KBr): 2984, 1697, 1461, 1276, 1157, 1043, 999 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (d, *J* = 7.03 Hz, 6 H), 2.09 (m, 4 H), 2.37 (m, 4 H), 3.46 (m, 2 H), 3.61 (m, 2 H), 4.07 (br s, 4 H), 4.36 (br s, 4 H), 6.15 (q, *J* = 7.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 19.9, 31.1, 45.6, 48.5 (br s, 2 C), 60.9, 174.9, 195.4.

Anal. Calcd for $C_{18}H_{28}N_4O_2S_4$: C, 47.93; H, 6.13; N, 12.16. Found: C, 47.58; H, 6.18; N, 12.25.

2.

Bis[1-(2-oxopyrrolidin-1-yl)ethyl]ethylenediamine-1,2-dicarbodithioate (2n)

Yield: 0.456 g (35%); yellow solid; mp 150–152 °C.

IR (KBr): 3313, 3183, 2978, 1664, 1527, 1264, 1069, 949 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.1 Hz, 6 H), 2.10–2.18 (m, 4 H), 2.49–2.61 (m, 4 H), 3.43–3.61 (m, 4 H), 4.08–4.16 (m, 4 H), 6.00–6.15 (m, 2 H), 9.78 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.1, 31.1, 42.4, 45.5, 54.2, 176.8, 194.0.

Anal. Calcd for $C_{16}H_{26}N_4O_2S_4$: C, 44.21; H, 6.03; N, 12.89. Found: C, 43.93; H, 5.75; N, 13.39.

Bis(dithiocarbamate) 2o
Yield: 1.07 g (70%); yellow solid; mp 138–141 °C.

IR (KBr): 3246, 1667, 1532, 1082, 944 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 7.13 Hz, 6 H), 2.08–2.49 (m, 8 H), 3.45 (m, 2 H), 3.59 (m, 2 H), 4.89–5.04 (m, 4 H), 5.97 (q, *J* = 7.1 Hz, 2 H), 7.30–7.42 (m, 4 H), 9.89 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 17.9, 31.0, 42.2, 50.1, 53.9, 127.6, 127.9, 128.7, 136.7, 176.6; C=S not observed.

Anal. Calcd for $C_{22}H_{30}N_4O_2S_4$: C, 51.73; H, 5.92; N, 10.97. Found: C, 51.71; H, 5.82; N, 11.03.

Acknowledgment

We are grateful to the Faculty of Chemistry, Kharazmi University (Tarbiat Moallem University) for supporting this work.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) *Chemistry in Alternative Reaction Media*; Adams, D. J.; Dyson, P. J.; Tavener, S. J., Eds.; Wiley-VCH: Weinheim, **2000**.
(2) (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140. (b) Li, M.; Cao, H.; Wang, Y.; Lv, X.-L.; Wen, L.-R. *Org. Lett.* **2012**, *14*, 3470. (c) Ananikov, V. P.; Beletskaya, I. P. *Org. Biomol.*

Chem. **2004**, *2*, 284. (d) Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744.
(3) (a) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1. (b) Tejedor, D.; González-Cruz, D.; Santos-Expósito, A.; Marrero-Tellado, J. J.; de Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2005**, *11*, 3502. (c) Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; and references cited therein.
(4) (a) Marinovich, M.; Viviani, B.; Capra, V.; Corsini, E.; Anselmi, L.; D'Agostino, G.; Nucci, A. D.; Binaglia, M.; Tonini, M.; Galli, C. L. *Chem. Res. Toxicol.* **2002**, *15*, 26. (b) Weissmahr, K. W.; Houghton, C. L.; Sedlak, D. L. *Anal. Chem.* **1998**, *70*, 4800.
(5) (a) Len, C.; Boulogne-Merlot, A. S.; Postel, D.; Ronco, G.; Villa, P.; Goubert, C.; Jeufrault, E.; Mathon, B.; Simon, H. *J. Agric. Food Chem.* **1996**, *44*, 2856. (b) Bergendorff, O.; Hansson, C. *J. Agric. Food Chem.* **2002**, *50*, 1092.
(6) (a) Lai, J. T.; Shea, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4298. (b) Duréault, A.; Gnanou, Y.; Taton, D.; Destarac, M.; Leising, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 2869. (c) Bathfield, M.; D'Agosto, F.; Spitz, R.; Charreyre, M. T.; Delair, T. *J. Am. Chem. Soc.* **2006**, *128*, 2546.
(7) (a) Tsuboi, S.; Takeda, S.; Yamasaki, Y.; Sakai, T.; Utka, M.; Ishida, S.; Yamada, E.; Hirano, J. *Chem. Lett.* **1992**, 1417. (b) Katritzky, A. R.; Singh, S.; Mahapatra, P. P.; Clemense, N.; Kirichenko, K. *ARKIVOC* **2005**, *(ix)*, 63.
(8) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley Interscience: New York, **1999**, 484.
(9) (a) Ziyaei-Halimehjani, A.; Porshojaei, Y.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 32. (b) Maddani, M.; Prabhu, K. R. *Tetrahedron Lett.* **2007**, *48*, 7151.
(10) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969.
(11) Ziyaei-Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747.
(12) Jamir, L.; Sinha, U. B.; Nath, J.; Patel, B. K. *Synth. Commun.* **2012**, *42*, 951.
(13) (a) Blanrue, A.; Wilhelm, R. *Synthesis* **2009**, 583. (b) Zhang, D.; Chen, J.; Liang, Y.; Zhou, H. *Synth. Commun.* **2005**, *35*, 521.
(14) Kumar, K. N.; Sreeramamurthy, K.; Palle, S.; Mukkanti, K.; Das, P. *Tetrahedron Lett.* **2010**, *51*, 899.
(15) (a) Thorn, G. D.; Ludwig, R. A. *The Dithiocarbamates and Related Compounds*; Elsevier: Amsterdam, **1962**. (b) Safak, C.; Erdogan, H.; Yesilada, A.; Erol, K.; Cimgi, I. *Arzneim.-Forsch.* **1992**, *42*, 123. (c) Aboul-Fadl, T.; El-Shorbagi, A. *Eur. J. Med. Chem.* **1996**, *31*, 165. (d) Cascio, G.; Lorenzi, L.; Caglio, D.; Manghisi, E.; Arcamone, F.; Guanti, G.; Satta, G.; Morandotti, G.; Sperning, R. *Farmaco* **1996**, *51*, 189. (e) Imamura, H.; Ohtake, N.; Jona, H.; Shimizu, A.; Moriya, M.; Sato, H.; Sugimoto, Y.; Ikeura, C.; Kiyonaga, H.; Nakano, M.; Nagano, R.; Abe, S.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem.* **2001**, *9*, 1571. (f) Gerhauser, C.; You, M.; Liu, J.; Moriarty, R. T.; Hawthorne, M.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 272. (g) Scozzafava, A.; Mastorlorenzo, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1887. (h) Ge, Z. M.; Li, R. T.; Cheng, T. M.; Cui, J. R. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 173. (i) Hou, X. L.; Ge, Z. M.; Wang, T. M.; Guo, W.; Cui, J. R.; Cheng, T. M.; Lai, C. S.; Li, R. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4214. (j) Huang, W.; Ding, Y.; Miao, Y.; Liu, M. Z.; Li, Y.; Yang, G. F. *Eur. J. Med. Chem.* **2009**, *44*, 3687.
(16) (a) Zhao, Y.; Pérez-Segarra, W.; Shi, Q.; Wei, A. *J. Am. Chem. Soc.* **2005**, *127*, 7328. (b) Ivachtchenko, A.; Kovalenko, S.; Tkachenko, O. V.; Parkhomenko, O. *J. Comb. Chem.* **2004**, *6*, 573.
(17) Ziyaei Halimehjani, A.; Marjani, K.; Ashouri, A. *Green Chem.* **2010**, *12*, 1306.
(18) (a) Saidi, O.; Ruan, J.; Vinci, D.; Wu, X.; Xiao, J. *Tetrahedron Lett.* **2008**, *49*, 3516. (b) Zhang, Y.; Jiang, J.; Chu, X.-Q.; Jiang, R.; Xu, X.-P.; Li, D. H.; Ji, S.-J. *Synlett* **2012**, *23*, 751. (c) Chen, G.-T.; Wang, C.-H.; Zhang, J.-G.; Wang, Y.; Zhang, R.; Du, F.-S.; Yan, N.; Kou, Y.; Li, Z.-C. *Macromolecules* **2010**, *43*, 9972.
(19) (a) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275. (b) Ziyaei Halimehjani, A.; Saidi, M. R. *Can. J. Chem.* **2006**, *84*, 1515. (c) Azizi, N.; Pourhasan, B.; Aryanasab, F.; Saidi, M. R. *Synlett* **2007**, 2797. (d) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634. (e) Yavari, I.; Hosseini, N.; Moradi, L.; Mirzaei, A. *Tetrahedron Lett.* **2008**, *49*, 4239.
(20) (a) Rafin, C.; Veignie, E.; Postel, M. S.; Len, C.; Villa, P.; Ronco, G. *J. Agric. Food Chem.* **2000**, *48*, 5283. (b) De Sousa, R.; Thurier, C.; Len, C.; Pouilloux, Y.; Barrault, J.; Jérôme, F. *Green Chem.* **2011**, *13*, 1129.
(21) Ramachandran, G.; Karthikeyan, N. S.; Giridharan, P.; Sathiyanarayanan, K. I. *Org. Biomol. Chem.* **2012**, *10*, 5343.

