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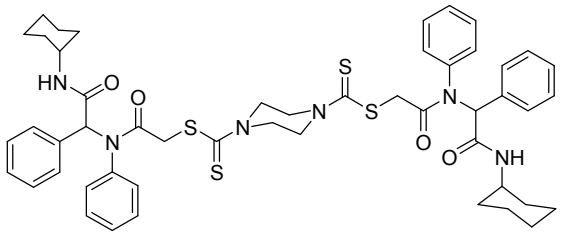


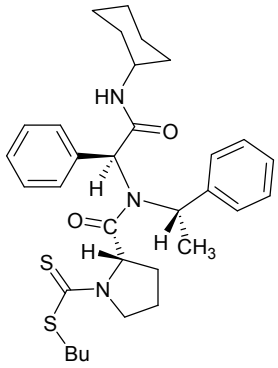


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# ARTICLE TYPE

# Synthesis of a new series of dithiocarbamate-linked peptidomimetics and their application in Ugi reaction

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

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Novel peptidomimetics containing the dithiocarbamate groups were synthesized *via* the Ugi reaction. Also, dithiocarbamates of natural amino acids were prepared and were used successfully in Ugi reaction to prepare novel peptidomimetics bearing amino acid and dithiocarbamate groups in single structure. In addition the prepared dithiocarbamates based on amino acids are converted to the corresponding amides.

Peptidomimetics are biologically important class of artificial small molecules. The term "peptidomimetics" include the modification of amino acid side chains, the introduction of constraints to fix the location of different parts of the molecule,[1] the development of templates that induce or stabilize secondary structures of short chains,[2] the creation of scaffolds that direct side-chain elements to specific locations, and the modification of the peptide backbone. Peptidomimetics are designed to circumvent some of the problems associated with several natural peptides like stability against proteolysis and poor bioavailability.[3] Certain other properties such as receptor selectivity or potency can be substantially improved. Hence a variety of peptide mimics are being developed to introduce drug-like character along with increased potency, target specificity and longer duration of action. To this end, several classes of peptidomimetics are tailored by replacing the native amide bond with various other tethers and are biologically scrutinized.[4] Peptidomimetics by inserting non-native linkages such as urea,[5] thiourea,[6] retro-amide,[7] carbamate,[8] nucleic bases[9], steroids[10]and heterocycles[11] have been reported extensively.

Among the methods for the multicomponent synthesis of peptides or amino acids, the Ugi reaction, is without any doubt the most widely exploited.[12] This powerful reaction involves a one-pot condensation of an amine, a carbonyl compound, a carboxylic acid, and an isocyanide to provide a substituted peptide-like product. Various modifications of the classical Ugi-4CR have been introduced. Those involved the varying of one of the components or the introduction of new functional groups leading to the synthesis of new derivatives of α-amino acyl amide derivatives with novel biological activities.

Dithiocarbamates are valuable compounds due to their use as versatile synthetic intermediates,[13] linkers in solid phase organic synthesis,[14] radical chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerizations,[15] and in molecular electronic devices.[16] Moreover, due to their biological activities as antihistaminic,[17]antibacterial,[18]and anticancer[19]agents and their vital role in agriculture as pesticides and fungicides,[20] development of convenient synthetic method for these compounds is important. Also due to coordination ability through sulfur atoms the dithiocarbamates have received much attention as ligand in recent years.[21]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.[22] Many proteins have cysteine and methionine residues and hence dithiocarbamate derivatives of α-amino acids may be valid models for the study of the coordination of proteins to metal ions.[23] In addition, dithiocarbamates have been developed as HIV-I NCp7 inhibitors.[24] Furthermore, in recent years several natural and unnatural amino acids containing dithiocarbamate side chains were synthesized and used in the construction of novel peptidomimetics.[25]

In continuation of our interest on the chemistry of dithiocarbamates,[26] herein we report a novel and efficient method for the synthesis of new peptidomimetics containing dithiocarbamate group via Ugi four-component (4CRs) reaction. Initially, we focused our attempt on the synthesis of a starting material containing the dithiocarbamate group suitable for Ugi reaction. For this purpose, a series of dithiocarbamates containing carboxylic acid were synthesized *via* one-pot three-component reaction of an amine, $CS_2$ and chloroacetic acid or chloropropionic acid as outline in Scheme 1.

<<Insert Scheme 1>>

Then, Ugi four-component coupling reaction between an amine, an aldehyde, a carboxylic acid containing dithiocarbamate group, and an isocyanide were used for preparation of novel peptidiomimetics containing the dithiocarbamate group. (Scheme 2) The reaction proceeded quite

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smoothly with good to excellent yields by employing methanol as solvent at room temperature. The results are summarized in Table 1. Carboxylic acids containing dithiocarbamate group **1a-g** were used successfully in this reaction. Also different isocyanides such as cyclohexyl isocyanide and *β*-naphthylisocyanide were used with high yields. Toluenesulphonylmethyl isocyanide was also used without suitable results. In addition, aromatic amines and aromatic aldehydes were used successfully in this process. Aliphatic amines and aldehydes gave low yield of products compare to the aromatic ones.

<<Insert Scheme 2>>

<<Insert Table 1>>

Also *bis*dithiocarbamate containing carboxylic acid based on piperazine **3** is synthesized and used in Ugi reaction to provide polyfunctional 1,4-disubstituted piperazine **4** as a symmetrical bivalent compound. (Scheme 3)

<<Insert Scheme 3>>

In continue, natural *α*-amino acids such as glycine, *dl*-alanine, and *S*-proline were used as amine surrogate for synthesis of dithiocarbamates **5a-e** as shown in Scheme 4. By using two equimolar of sodium hydroxide as promoter, good to excellent yields of product **5a-e** were obtained. Primary alkyl halides such as benzyl chloride and butyl bromide were used successfully in this process. Only the dithiocarbamic acid ester was obtained and no ester of carboxylic acid was observed. The results are summarized in Scheme 4. To the best of our knowledge it is the first report on the synthesis of dithiocarbamates from amino acids without any protection. In the case of *S*-proline no epimerization was observed.

<<Insert Scheme 4>>

The prepared dithiocarbamic acid esters of amino acids **5a-e** have been successfully used in the Ugi reaction to produce new peptidomimetics containing the natural amino acids and dithiocarbamate group **6a-n.**The results are summarized in Table 2. As shown in Table 2, electron–donating and –withdrawing groups on the aldehyde component do not affect the reaction yield. By using ethanolamine as amine surrogate in this reaction, the product **6g** was obtained in 40% yield that contain the hydroxyl group which allow further construction in the structure. Also, 2-chloroacetaldehyde was successfully used as carbonyl source in this reaction to prepare **6j** in 45% with a potential group for displacement by several nucleophiles. In addition to aniline derivatives, (*S*)-1-phenylethylamine was used in this reaction to prepare the novel peptidomimetic with three stereogenic centers as mixture of diastereomers (**6k** and its diastereomer). Using the optically active starting materials does not have significant effect on the diastereoselectivity of reaction.[27] Recrystalization of mixture of diastereomers in ethanol afford **6k** in 33% isolated yield with *R* configuration on newly created stereogenic center which was confirmed by NOE analyses. Structure of all products was fully characterized using $^{1}H$ and $^{13}C$ NMR, CHN analyses.

<<Insert Table 2>>

Recently we have shown that dithiocarbamates are suitable building blocks for synthesis of thioureas.[28] For this purpose, reaction of dithiocarbamates **5c-e** with aromatic amines such as aniline, 4-chloroaniline, 3,4-dichloroaniline, 4-methylaniline and 1-naphthylamine was carried out in solvent-free condition at 100 °C as outline in Scheme 5. Amides **7a-h** were obtained with excellent yields as the only product and no thiourea **8** was obtained. The results are summarized in Table 3. The proposed mechanism for synthesis of the amide products is outlined in Scheme 6. The amide bond formation was promoted by dithiocarbamate group *via* formation of thiazol-5(4*H*)-one as intermediate and subsequent addition of aniline to this intermediate. This reaction is not possible with **5a-b**.

<<Insert Scheme 5>>

<<Insert Scheme 6>>

<<Insert Table 3>>

In conclusion, we have presented an efficient procedure for the synthesis of novel peptidomimetics containing the dithiocarbamate groups *via* Ugi four components reaction. Also we have shown that dithiocarbamates prepared with natural amino acids can be simply used in Ugi reaction as acid surrogate for synthesis of peptidomimetics bearing amino acids and dithiocarbamate group in single structure. In addition the prepared dithiocarbamate based on amino acids are converted to the corresponding amides without using any catalyst and harsh conditions. It is notable that dithiocarbamates are well-known group for protection of the amino group of amino acids.[29] So by simple deprotection, the amino group can be furnished in the structure of Ugi adducts for further constructions and applications.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [Full experimental details, characterization data, copy of $^{1}H$ and $^{13}C$ NMR spectra for all compounds]. See DOI: 10.1039/b000000x/

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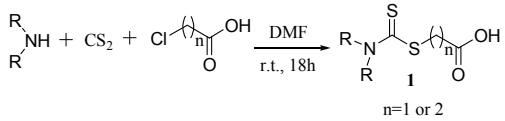
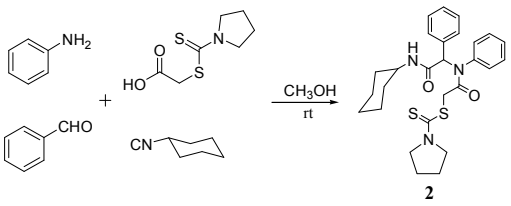


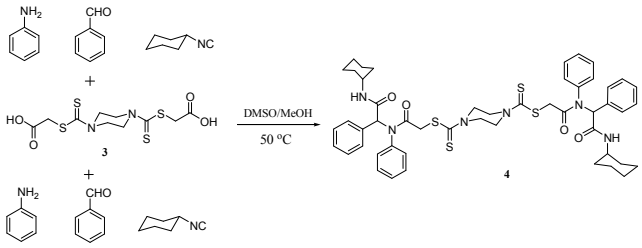

| amine | n | product | yield (%)[a] |
|---|---|---|---|
| diethyamine | 1 | 1a | 55 |
| pyrrolidine | 1 | 1b | 70 |
| | 2 | 1c | 68 |
| piperidine | 1 | 1d | 60 |
| | 2 | 1e | 60 |
| morpholine | 1 | 1f | 65 |
| azepane | 1 | 1g | 52 |

[a] isolated yield.

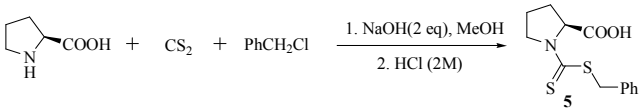
**Scheme1** Synthesis of dithiocarbamates




**Scheme 2** Synthesis of Ugi adduct containing the dithiocarbamate group



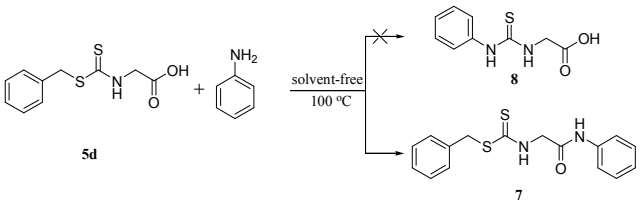

**Scheme 3** Synthesis of *bis*Ugi adduct based on piperazine



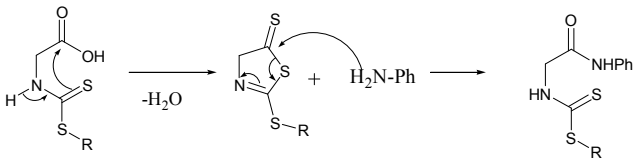

| Amino acid | alkyl halide | product | Yield (%)[a] |
|---|---|---|---|
| *S*-proline | benzyl chloride | **5a** | 95 |
| *S*-proline | butyl bromide | **5b** | 81 |
| *dl*-alanine | benzyl chloride | **5c** | 70 |
| Glycine | benzyl chloride | **5d** | 90 |
| Glycine | butyl bromide | **5e** | 83 |

[a] Isolated yield.

**Scheme 4** Synthesis of novel peptidomimetics containing dithiocarbamate group




**Scheme 5** Amide bond formation promoted by dithiocarbamate group




**Scheme 6** Proposed mechanism for amide bond formation

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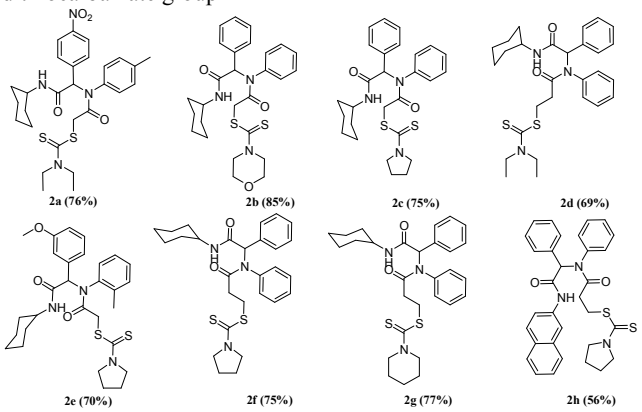
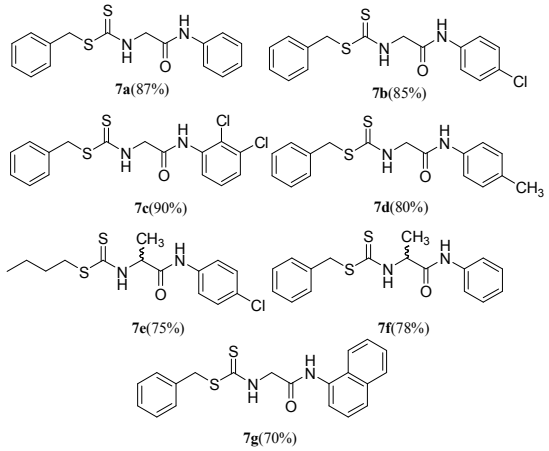
**Table 1** Diversity in the synthesis of Ugi adducts containing dithiocarbamate group[a]



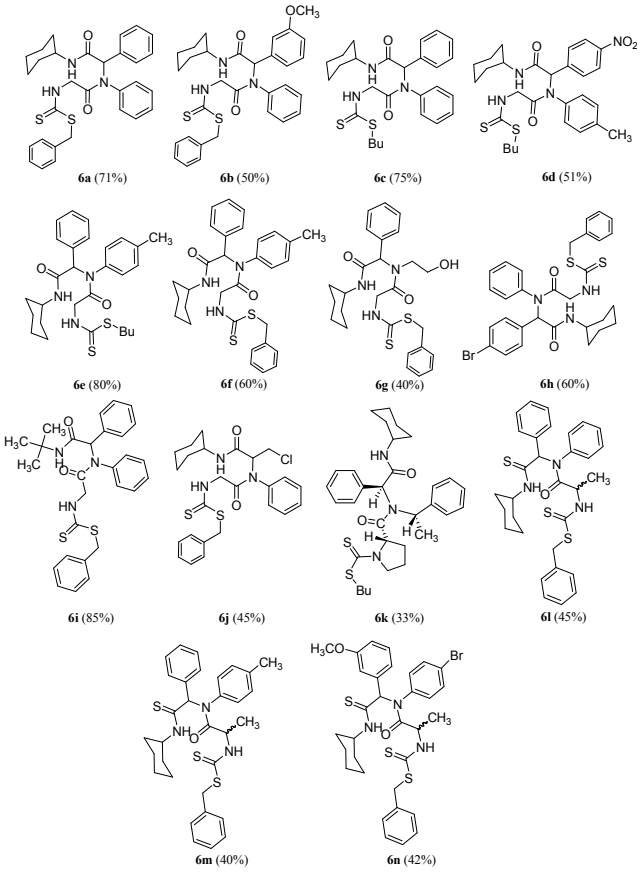

[a] Isolated yield

**Table 3** Diversity in the synthesis of amides 7 with the reaction of amino acid based dithiocarbamates with aromatic amines




[a] Isolated yield.

**Table 2** Diversity in the synthesis of novel peptidomimetics containing natural amino acids and dithiocarbamate groups [a]




[a] Isolated yield.