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A straightforward approach towards thiazoles and endothiopeptides *via* Ugi reaction†

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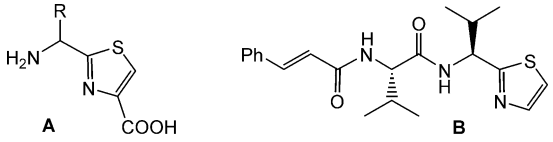
Endothiopeptides can easily be obtained *via* Ugi reaction using thio acids as acid components. If isonitriles with an acetal group are applied, the endothiopeptides can directly be converted into thiazoles using TMSCl–NaI under microwave irradiation.

Introduction

Peptides with backbone modifications are highly interesting from a pharmaceutical point of view and have therefore attracted considerable interest in recent years.[1] The replacement of proteolysable amide bonds has been an especially successful strategy in the design of novel enzyme inhibitors.[2] Thioamides, for example, have been used as amide bond surrogates in a number of biologically active peptides such as cyclosporine,[3] enkephaline[4] and others.[5] They have also been incorporated into inhibitors of carboxypeptidase A,[6] triosephosphate isomerase,[7] angiotensin-converting enzyme[8] or HIV-1 protease.[9] Exchange of a normal amide bond by a thioamide bond results in a higher proteolytic stability,[6,8] and also a higher rotation barrier around the C–N bond,[10] which has an influence on the conformation, especially of cyclic peptides.[7] If the thioamide bond is located between an amino acid/peptide and a serine, cyclisation can occur giving rise to thiazoline amino acids,[11] which can be oxidized to thiazole amino acids **A**.[12] Such thiazolines and thiazoles are widely found in nature, especially in cyclic peptides of marine origin.[13] Thiazole amino acids of type **A** are generally located in the middle of a peptide chain, while unsubstituted thiazoles are found at the C-terminal position of several natural products,[14] such as dolastatin 18[15] or the virenamides (**B**).[16]



Virenamid E

Based on the high pharmaceutical potential of these peptides, many synthetic studies have been undertaken towards their synthesis. Endothiopeptides, containing a thioamide bond, can be obtained either by direct thionation with Lawesson's reagent[17] or *via* thioacylation with alkyl dithioesters[18] and thio acids or derivatives.[19] Ring opening of azirines with thio acids gives direct access to endothiopeptides containing quaternary amino acids such as Aib.[20] The use of enzymatic coupling of endothiopeptide methyl esters with the amino terminus of peptides has also been reported.[21]

Besides the "classical protocol" *via* cyclisation mentioned above, the thiazole amino acids of type **A** can also be obtained in a combinatorial way *via* Ugi reaction using thiocarboxylic acids and a suitable isonitrile (Scheme 1).[22] In principle, an endothiopeptide should be formed as an intermediate, but this could not be isolated under the reaction conditions used.

† Electronic supplementary information (ESI) available: preparation and analytical/spectroscopic data of all peptides **2** and **3** as well as the thiazoles **6**. See http://dx.doi.org/10.1039/b507028g

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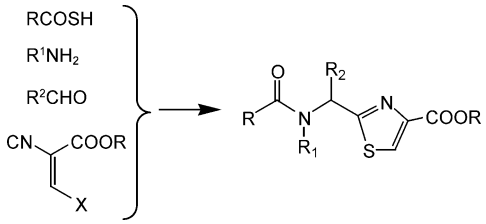
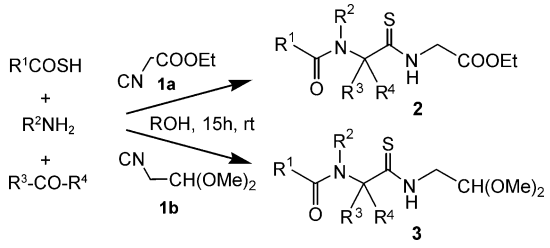


Scheme 1 Thiazole synthesis *via* Ugi reaction.

Results and discussion

Our group has been involved in amino acid and peptide syntheses for several years,[23] also taking advantage of the Ugi reaction[24] as a straightforward approach to obtain complex peptide structures.[25] In combination with ring closing metathesis, this approach was also used for the synthesis of cyclic peptides.[26] Herein we report on the application of Ugi reactions for the synthesis of endothiopeptides and their conversion into thiazoles. We began our investigations concerning the endothiopeptide synthesis with the commercially available thio acids, thio acetic acid and thio benzoic acid, using benzylamine as standard amine component (Scheme 2). Ethyl isocyanoacetate **1a** was chosen because it gives rise directly to glycine incorporated endothiodipeptides **2**. As carbonyl components we chose aliphatic and aromatic aldehydes as well as cyclohexanone as a representative ketone.



Scheme 2 Synthesis of endothiopeptides *via* Ugi reaction.

Several examples are given in Table 1. In general, the best results were obtained with sterically demanding aldehydes such as pivalaldehyde (entries 3, 4), which are in good agreement with previous observations made with carboxylic acids. Thio benzoic acid was found to be slightly superior to thio acetic acid, but the overall yields were very good, and the products were formed in relatively pure form.

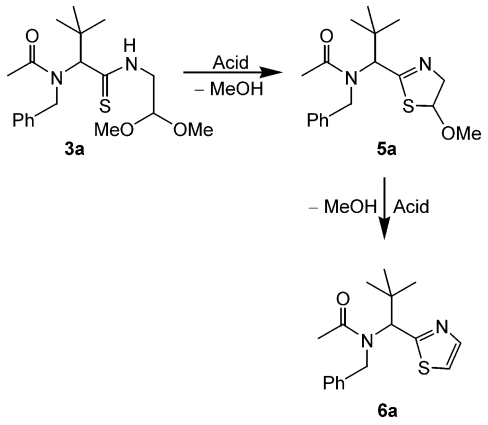
Especially in the reactions with pivalaldehyde, the products showed a high tendency to crystallise, in general, precipitated directly from the reaction mixture. Replacing benzylamine by ammonia (entries 7, 8) resulted in a significantly lower yield.

Table 1 Endothiopeptides obtained by Ugi reaction

Entry	R^1	R^2	R^3	R^4	Isonitrile	Peptide	Yield (%)
1	Me	Bn	iPr	H	**1a**	**2a**	68
2	Ph	Bn	iPr	H	**1a**	**2b**	82
3	Me	Bn	*t*Bu	H	**1a**	**2c**	72
4	Ph	Bn	*t*Bu	H	**1a**	**2d**	89
5	Ph	Bn	Ph	H	**1a**	**2e**	65
6	Ph	Bn		$-(CH_2)_5-$	**1a**	**2f**	55
7	Me	H	*t*Bu	H	**1a**	**2g**	31
8	Ph	H	*t*Bu	H	**1a**	**2h**	35
9	Me	Bn	*t*Bu	H	**1b**	**3a**	81
10	Me	Bn	iPr	H	**1b**	**3b**	51
11	Ph	Bn	*t*Bu	H	**1b**	**3c**	71
12	Me	Bn		$-(CH_2)_5-$	**1b**	**3d**	55
13	Me	Me	*t*Bu	H	**1b**	**3e**	92
14	Ph	Me	*t*Bu	H	**1b**	**3f**	80
15	Ph	H	*t*Bu	H	**1b**	**3g**	71

Ammonia is known to be a marginal substrate for Ugi reactions, undergoing a wide range of side reactions.[25b,d]

Encouraged by the good results obtained with benzylamine we also varied the isonitrile component. Anticipating application to subsequent thiazole synthesis, we chose the related acetal **1b**. The yields were comparable to the results obtained with isocyanoacetate **1a** (entries 9 to 15). With this isonitrile we also varied the amine component. Allylamine, for example, gave yields in the range of 76–90%, but the products obtained were unstable and decomposed on standing, some of them rapidly. But with methylamine, which gives direct access to *N*-methylated peptides, the results were excellent (entries 13, 14), and even ammonia gave the expected product in good yield (entry 15). With these endothiopeptides **3** in hand, we began our investigations towards the thiazole synthesis. In principle, under acidic conditions, the nucleophilic sulfur should attack the acetal moiety providing thioacetal **5**, which would then undergo elimination yielding the expected thiazole **6** (Scheme 3). As a test system we chose **3a** and investigated the influence of the acid used on the acetal cleavage (Table 2). Unfortunately, the reaction stopped on the state of the thiazoline **5a**, and no elimination was observed under all conditions used.



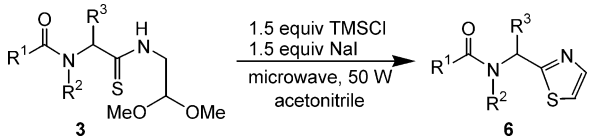
Scheme 3 Two step conversion of endothiopeptides into thiazoles.

Table 2 Acidic cyclisation of **3a**

Acid	Solvent	Reaction time	Yield **5a** (%)
10 mol% TsOH	Acetone	72 h	75
1 equiv $TiCl_4$	Ether	4 h	75
50% TFA	$CHC1_3$	3 h	86
1 equiv BF_3OEt_2	Ether	4 h	94
10 mol% HCl	CH_2C1_2	15 h	95

With BF_3 and HC1 a clean conversion was observed, and the thiazoline was obtained in nearly quantitative yield. We therefore tried to generate the thiazole **6a** from thiazoline **5a**. According to Jacobi *et al.*[27] methanesulfonic acid should be the acid of choice for this purpose. Indeed, with this acid we were able to isolate some thiazole **6a**, albeit in only 17% yield, which was close to the results reported in the literature. Unfortunately, decomposition was the major problem, probably the thiazole is not stable under these relatively drastic acidic conditions. We therefore thought that cleavage of the thioacetal to the thiosemiacetal might be an interesting option. This brought us to a reagent which is generally used for ether cleavage: TMSCl–NaI as a substitute for TMSI.[28] With this reagent combination in acetonitrile, the required thiazole **6a** indeed was obtained in 55% yield. Prolonging the reaction time unfortunately did not result in higher yields but rather complete decomposition. This clearly indicates that it is the lability of the thiazole that causes the problems. Obviously it is important to shorten the reaction time to get good results, and we therefore investigated the same reaction under microwave irradiation. After 10 min (50 W) a complete conversion of the thiazoline **5a** was observed and thiazole **6a** was obtained in 80% yield.

In principle both steps, the thiazoline and the thiazole formation, proceed under (Lewis) acidic conditions. This caused us to subject the Ugi products **3** directly in the microwave to the TMSCl–NaI treatment (Scheme 4) and the results are summarized in Table 3. A few thioamides such as the *N*-allyl derivatives mentioned before, or the derivative **3d** were not stable and decomposed completely, but the others gave the expected thiazoles **6** in good to excellent yield.



Scheme 4 Direct conversion of endothiopeptides into thiazoles.

Table 3 Thiazoles obtained by microwave reaction

Acetal	Thiazole	Time (min)	Yield (%)
3a	**6a**	30	80
3b	**6b**	10	87
3c	**6c**	5	91
3e	**6e**	30	66
3g	**6g**	15	91

Conclusion

In conclusion we have shown that the application of thio acids in Ugi reactions gives rise to endothiopeptides in one step with the option of combinatorial synthesis. If suitable isonitriles are used, these endothiopeptides can be converted into peptidic thiazoles also in one step under microwave irradiation.

Experimental

Preparation of isonitrile 1b

Aminoacetadehyde dimethylacetal (21.0 g, 0.20 mmol) was dissolved in ethyl formate (200 mL) and refluxed overnight. After cooling to room temperature, the solvent was removed *in vacuo.* The *N*-formylaminoacetaldehyde dimethylacetal was obtained as a pale yellow liquid (26.0 g, 0.19 mol, 98%).

This formamide (20.0 g, 0.15 mol), was dissolved in CH_2C1_2 (200 mL) together with triethylamine (45.5 g, 0.45 mol) and the reaction mixture was cooled to 0 °C before $POC1_3$ (23.0 g, 0.15 mol) was added dropwise to the solution. The mixture was allowed to warm to room temperature and after stirring for 1 h at room temperature, Na_2CO_3 solution (150 mL, 20 g in 100 ml water) was added and the mixture was stirred for another hour at room temperature. Then water was added, the layers were separated, and the organic layer was washed 3 times with water. After drying the organic layer over Na_2SC_4, the solvent was removed *in vacuo.* Distillation in high vacuo ($kp_{0.15}$ = 50 °C) provided the isonitrile **1b** as a colourless liquid (9.76 g, 85.0 mmol, 57%). ^{1}H NMR (500 MHz, $CDC1_3$): δ = 3.36 (s, 6H), 3.44 (d, J = 5.7 Hz, 2H), 4.54 (t, J = 5.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDC1_3$): δ = 43.5, 54.4, 101.0, 158.5.

General procedure for Ugi reactions with thio acids

The aldehyde (*n* mmol) and the amine (*n* mmol) were dissolved in alcohol (*n* mL, ethanol for Ugi products **2** and methanol for Ugi products **3**) and stirred for 15 min at room temperature. Then the reaction mixture was cooled to 0 °C and the thio acid (*n* mmol) was added followed by the isonitrile (*n* mmol). The ice-bath was removed and the mixture was stirred overnight at room temperature. Then CH_2Cl_2 was added and the organic layer was washed twice with saturated Na_2CO_3 solution and 1 M $KHSO_4$ solution. After drying the organic layer over Na_2SC_4, the solvent was removed *in vacuo* and the crude product was purified by column chromatography and/or recrystallisation.

Ethyl [2-(acetyl-benzylamino)-3-methyl-thiobutyryl]-glycinate (2a)

According to the general procedure for thio Ugi reactions, **2a** was obtained after purification by column chromatography (hexanes–EtOAc = 6 : 4) in a 2.00 mmol range as a yellow oil in 68% yield. ^{1}H NMR (500 MHz, $CDC1_3$): δ = 0.67 (d, J = 6.1 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 2.10 (s, 3H), 2,81 (bs, 1H), 4.18 (q, J = 7.0 Hz, 2H), 4.29 (dd, J = 13.1, 5.2 Hz, 2H), 4.35 (d, $J_{4,5}$ = 4.9 Hz, 1H), 4.57 (s, 2H), 7.16–7.26 (m, 5H), 7.97 (bs, 1H). ^{13}C NMR (125 MHz, $CDC1_3$): δ = 14.1, 20.3, 28.3, 47.2, 61.6, 125.9, 127.5, 128.7, 138.7, 168.6, 173.8, 202.6. HMRS (CI): calcd. for $C_{18}H_{26}N_2O_3S$ ([M]$^+$), 350.1664; found, 350.1653.

N-(2,2-Dimethoxy-ethyl)-2-(acetyl-benzylamino)-3,3-dimethyl-thiobutyric acid amide (3a)

According to the general procedure for thio Ugi reactions, **3a** was obtained after recrystallisation from *tert*-butyl-methylether in a 2 mmol range as white rhombic crystals in 81% yield, mp 110–112 °C. ^{1}H NMR (500 MHz, $CDC1_3$): δ = 1.06 (s, 9H), 2.13 (s, 3H), 3.33 (s, 6H), 3.70 (m, 2H), 4.23–4.54 (m, 4H), 7.19–7.26 (m, 5H), 10.82 (bs, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 23.4, 28.5, 38.2, 54.3, 54.7, 102.2, 129.6, 176.5, 201.5. HRMS (CI): calcd. for $C_{19}H_{30}N_2O_3S$ ([M]$^+$), 366.1978; found, 366.1978. Elemental analysis: $C_{19}H_{30}N_2O_3S$ (364.51) calcd.: C 62.61 H 7.74 N 7.69; found: C 62.10 H 7.49 N 7.57.

2-[l-(Acetyl-benzylamino)-2,2-dimethyl-propyl]-5-methoxy-4,5-dihydrothiazole (5a)

Endothiopeptide **3a** (1.10 g, 3.00 mmol) was dissolved in CH_2C1_2 (50 mL) and conc. HC1 (250 µL, 0.30 mmol) was added dropwise. The reaction mixture was stirred overnight. Then it was washed twice with saturated $NaHCO_3$ solution and once with brine. The organic layer was dried over $NaSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (hexanes–EtOAc = 7 : 3) and thiazoline **5a** was obtained as a white solid (953 mg, 2.80 mmol, 95%), mp 71–73 °C. ^{1}H NMR (500 MHz, $CDC1_3$): δ = 1.02 (s, 4.5H), 1.05 (s, 4.5H), 1.85 (s, 1.5H), 1.89 (s, 1.5H), 3.14 (s, 1.5H), 3.18 (s, 1.5H), 3.25 (dd, J = 16.7, 6.0 Hz, 0.5H), 4.08 (dd, J = 16.7, 6.0 Hz, 0.5H), 4.25 (dd, J = 17.0, 13.0 Hz, 1H), 4.50 (dd, J = 27.4, 17.7 Hz, 1H), 5.25 (m, 2H), 5.63 (s, 0.5H), 5.70 (s, 0.5H), 6.93–7.19 (m, 5H). ^{13}C NMR (125 MHz, $CDC1_3$): δ = 23.7, 23.9, 28.6, 38.5, 39.1, 51.3, 41.4, 56.6, 57.2, 61.1, 61.9, 73.2, 73.4, 92.8, 93.2, 126.3, 127.1, 127.4, 127.6, 129.3, 139.6, 139.9, 174.0, 174.4. HRMS (CI): calcd. for $C_{18}H_{26}N_2O_2S$ ([M + H]$^+$), 335.1793; found, 335.1784.

General procedure for thiazole synthesis using microwaves

The endothiopeptide **3** (*n* mmol) was dissolved in acetonitrile (10 *n* mL). Then TMSC1 (1.5 *n* mmol), and NaI (1.5 *n* mmol) were added. The reaction mixture was irradiated in a sealed tube in a focused microwave oven (CEM Discover) at 50 Watt for the specified time. Water and CH_2C1_2 were added to the mixture, the layers were separated and the organic layer was washed with 10% $Na_2S_2O_3$ solution. After drying the organic layer over Na_2SC_4, the solvent was removed *in vacuo* and the crude product was purified by column chromatography.

2-[l-(Acetyl-benzylamino)-2,2-dimethyl-propyl]-thiazole (6a)

After the general procedure for thiazole synthesis using microwaves, **6a** was obtained after purification by column chromatography (hexanes–EtOAc = 7 : 3) in a 0.10 mmol range as a white solid in 80% yield, mp 108–110 °C. ^{1}H NMR (500 MHz, $CDC1_3$): δ = 1.06 (s, 9H), 1.86 (s, 3H), 4.60 (d, J = 17.3 Hz, 1H), 5.42 (d, J = 17.4 Hz, 1H), 6.19 (s, 1H), 6.61 (d, J = 6.9 Hz, 1H), 6.99–7.08 (m, 5H), 7.51 (d, J = 4.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDC1_3$): δ = 22.7, 27.9, 38.3, 50.4, 59.5, 118.6, 125.1, 126.4, 128.3, 138.7, 142.9, 165.7, 172.8. HRMS (CI): calcd. for $C_{17}H_{22}N_2OS$ ([M]$^+$), 302.1453; found, 302.1452. Elemental analysis: $C_{17}H_{22}N_2OS$ (302.45) calcd.: C 67.51 H 7.33 N 9.26; found: C 67.07 H 7.26 N 9.05.

Acknowledgements

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