Preparation of Pseudopeptides Building Blocks with Retro-Thioamide Bond Mediated *via* Thiocarbamoyl *Meldrum*'s Acid

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Abstract: An easy and efficient synthesis of pseudo tripeptide containing a thiomalonamide moiety was developed. Isothiocyanate derivatives of amino acids react smoothly with 2,2-dimethyl-1,3-dioxane-4,6-dione yielding new thiocarbamoyl *Meldrum*'s acids. Thermal decomposition of this new *Meldrum*'s acid derivatives generate thiocarbamoyl ketenes, which acylate amino acid esters to give pseudo tripeptides.

Key words: amides, peptides, acylation, ketenes, *Meldrum*'s acid.

Introduction. - It is a matter of course that peptides play an essential and significant role in virtually all biochemical processes of living beings. One can, at this point, cite the widespread use in medicine of large peptides derived from biotechnology such as, for example, well known interferons, erythropoetin, insulin, etc., to very short ones, like oxytocine, enkephalin, or tuftsine, although all peptides with long or short chains possess the same drawback, that is, their rapid enzymatic degradation in living organisms [1]. As a consequence, a lot of modyfications of the peptides backbone were applied. For example, an amide bond could be replaced by a: retroinverso hydroxyethylene [2], hydroxyethylene [3], ketomethylene [4], aminomethylene [5], retro-inverso [6] or thioamide moiety [7].

In our researches we focused on the possibility of obtaining a scaffold of retro modified petides, which also contain a thioamide modification introduced regioselectively.

One of the aproaches to retro modification of peptide is based on the introduction of a malonodiamide moiety in the structure of the molecule. Implementation of this task requires the use of any malonic derivative. Most of the synthesis of malonodiamide type of retro modified peptides uses as a starting material mono or diesters of malonic acid. This is incorporated into the peptide chain by the typical condesation procedures [8]. In another orginal aproach, *Meldrum*'s acid was used as a equivalent of malonic acid; such a strategy allows applying the acylating properties of 2,2-dimethyl-1,3-dioxane-4,6-dione to facilitate preparation of the first amide bond, whereas the second amide bond was obtained by the classical method [9].

Recently we have demonstrated that carbamoyl *Meldrum*'s acid derivatives in the presence of TMSCl may also acylate efficiently also more basic nucleophiles as aliphatic secondary amines [10] in contrast to the work of *Pak* and co-workers [11]. In such a synthetic strategy 5-[hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones during the thermal decomposition are a source of carbamoyl ketenes which can acylate a broad spectrum of nucleophilic reagents.

At this moment, we propose that sulphur analogues of carbamoyl *Meldrum*'s acid **1** could be used for the preparation of modified peptides containig a retro-thioamide bond. Realization of this goal requires the following: firstly, preparation of

enough stable compounds of type **1** where R^1 is the rest of an amino acid, secondly generation of thiocarbamoyl ketenes from **1,** and finally acylation of C-protected amino acids with the new thiocarbamoyl ketenes (*Scheme 1*).

Results and Discusion. - At the begining we decided to check if the "non-peptide" sulphur derivative 5-[mercapto(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1a**) will be a good source of thiocarbamoyl ketenes and if the acylation of nucleophiles with this ketenes will be possible in the usual way.

In the first experiments, we heated in boiling ethylbenzene 1 equiv. of **1a** in the presence of 2 equiv. of aniline. The process was stopped when TLC analysis showed decay of all starting *Meldrum*'s derivative. From the reaction mixture we isolated 3-anilino-*N*-phenyl-3-thioxopropanamide (**3aa**) in 79% yield (*Table, Entry 1*). In the next very similar experiment we used *p*-toluidine as a trapping nucleophile. The result of this experiment was somewhat perplexing as from the reaction mixture we isolated an inseparable mixture of two very similar thiomalonamides **3ab** and **3xb** (*Entry 2*).

The unforeseen formation of a second product **3xb** may occur on two paths: first by the vinylic substitution on the starting carbamoyl *Meldrum*'s acid derivative, followed by decomposition to thiocarbamoyl ketene and its reaction with the nucleophil or by a second path involving transamidation of the initially formed thioamide **3ab**. (*Scheme 2*).

In order to decide which of the paths leading to the formation of thioamide **3xb** we decided to perform two experiments. In the first one we heated in boiling ethylbenzene, 1 equiv. of 3-anilino-N-phenyl-3-thioxopropanamide **3aa** which was previously prepared on the independent way, with 2 equiv. of *p*-toluidine for 1 h. The ^{1}H-NMR spectra of such a reaction mixture showed formation of the 3-[(4-methylphenyl)amino]-N-phenyl-3-thioxopropanamide **3xb**. The ratio of both thiomalonoamides **3ab** and **3xb** was estimated on the basis of integration of the malonic CH_2 group and revealed that **3xb** through classical transamidation arise only in 9% yield while in the reaction of **1a** with toluidine **3xb** was formed with 16% yield within only 35 min. In the second performed experiment, we heated **1a** with a 15-fold excess of *p*-toluidine in CH_2Cl_2 as a low boiling solvent in order to ensure a non thermolytic condition, to check if the vinylic substitution would be the

predominant reaction. However, we observed only unreacted starting material in the mixture. The above facts strongly indicate that **3xb** arise on both reaction paths, but higher yields of transamidation product are obtained from the reaction where the starting material was **1a** and suggests that vinylic substitution at **1a** is a faster reaction than classical transamidation in already formed thiomalonamide.

The source of complications of the experiment with **1a** are connected with the properties of aromatic amines as a moderately good leaving group. Hence, in the next experiments we used 5-[mercapto(methylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1b**) (*Entries 3-5*). Application of the methylamino derivative allows obtaining thiomalonoamides with good yields without transamidation products; these experiments confirmed that thiocarbamoyl ketens can be generated from **1** and trapped by nucleophiles.

In the next step of our research, we elaborated a synthesis of compounds **1** with another substitutent R^1 than an alkyl or aryl group, means the Gly and Val derivatives **1c,d**, which after thermolysis in the presence of a nucleophile would be an equivalent of retro-thioamide dipeptides GlyΨ(NHCS)Gly or ValΨ(NHCS)Gly [12]. For our purposes, we synthesised isothiocyanate derivatives of acetic and isovaleric acid **4c,d** using the method described in [13]. These isocyanates were used for the preparation of *Meldrum*'s acid derivatives using a modification of the procedure introduced by *Pak* [11]. We obtained new carbamoyl *Meldrum*'s acid derivatives **1c,d,** however, it should be stressed that this new derivatives were much less stable than ordinary *Meldrum*'s acid derivatives and decomposed when trying to purify or standing at room temperature. Hence, for our reactions we have used freshly prepared crude compounds **1c,d** (*Scheme 3*).

As a first experiments with the new carbamoyl *Meldrum*'s acid derivatives we performed a reaction of 1 equiv. of **1c** with 1 equiv. of toluidine. The reaction was heated in boiling ethylbenzene up to complete decomposition **1c**, and we obtained a dark-brown mixture with a lot of tar. TLC analysis revealed the presence of a complicated mixture of compounds. We repeated this experiment using 1,2-dichloroethane as a lower boiling solvent which increased the reaction time but allowed to obtain the required thiomalonoamide **3cb** with 68% yield (*Entry 6*).

Encouraged by the positive results of this experiment, we conducted a series of reactions in order to obtain the desired pseudopeptides with thiomalonoamide residue. We reacted in boiling 1,2-dichloroethane 1 equiv. of **1c,d** in the presence of amino acid hydrochloride. From the reactions mixtures we isolated pseudotripeptides in good yields (*Entries 6-12*). We also performed one experiment in tolune as a higher boiling solvent to check if it was possible to reduce the time required for completion of the reaction (*Entry 9).* Indeed, the reaction time was shortened; however the yield was little lower. For this reason, for the remaining experiments we used only less harsh conditions.

As one can see, the prepared pseudopeptides **3** are termined with carboxylic groups on both sides. For practical application, pseudopeptide building blocks terminated with an amino group on one side more useful would be [14]. In order to achive this target, we used monoacylated ethylenediamine as a trap for thiocarbamoyl ketenes. However, as a result of the first experiment, carried out with **1d** and the *N*-(2-aminoethyl)acetamide (**2i**), we obtained the pseudotripeptide in low yield (*Entry 14*). In this case we again observed the previously noticed rule [10] that less basic nucleophiles, means esters of aminoacids, react with better yield than more basic ones, *e.g.* derivative of ethylenediamine.

Based on our previous experiences with acylation of amines by ketenes generated form *Meldrum*'s acid derivatives, we proposed the use of TMSCl as a successful solution of this problem. From the reaction mixture formed by heating **2i** with **1c** or **1d** in DCE in the presence of 2 eqiv. of TMSCl we isolated retro-thiotripeptides **3ci** and **3di** in high yields. Additionally, we repeated the experiment beetwen **1c** and alanine methyl ester hydrochloride in the presence of TMSCl, and in this case, in accordance with our predictions, we did not observe an increase of yield (*Entry 13*).

In summary, we developed a new one pot method for the preparation of retro-thioamide modified peptides, based on thermolysis of new *Meldrum*'s acid derivatives. It should be stressed that our method allows the concurrent introduction of two modifications, *i.e.* the regioselective introduction of a thioamide and a retroamide moiety.

Experimental Part

General. All of the org. solvents used in this study were dried on appropiate drying agents and distilled prior to use. Commercially available reagents: from *Sigma-Aldrich*. TLC: *Merck Kieselgel 60 F_{254}.* Flash chromatography: *Zeochem ZEOprep 60/40-63*. M.p: *Warsztat Elektromechaniczny W-wa;* uncorrected. NMR Spectra: *Varian Unity Plus 500* (^{1}H: 500 MHz, ^{13}C: 125 MHz), *Varian Gemini 200* (^{1}H: 200 MHz, ^{13}C: 50 MHz); chemical shifts (δ) in ppm rel. to internal Me_4Si; coupling constants J in Hz. High-resolution (HR) MS: *MicroMas Quattro LCT* mass spectrometer. Commercially unavailable reagents were prepared using literature procedures as follows: 5-[Mercapto(phenylamino)methylene]-2,2-dimethyl -1,3-dioxane-4,6-dione (**1a**) [15], amino acids isothiocyanates [13].

5-[Mercapto(methylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1b**). To a sol. of *Meldrum*'s acid (0.72 g, 5 mmol) in dry DMF (2 mL) in a glass ampoule, Et_3N (1.4 mL, 10 mmol) was added. Methylisothiocyanate (0.365 g, 5 mmol) was added, and the ampoule was sealed. The ampoule was placed in the bath for 24 h at 40°. The mixture was poured into ice-cold aq. 2 M HCl (15 mL). The solid precipitate was filtered and washed with cold H_2O. The precipitate was dissolved in AcOEt (30mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. Crystallization from AcOEt/hexan gave 0.400 g 37 % **1b**. M.p. 99-101°. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.72 (*s*, 6 H); 3.16 (*d*, *J* = 5.0, 3 H); 11.32 (br. *s*, 1 H); 13.40 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.5, 32.1, 82.8, 104.7, 163.4, 170.8, 182.1. HRMS (ESI): calcd for $C_8H_{11}NO_4SNa$ $[M + Na]^+$: 240.0305; found: 240.0331

5-(Mercapto{[(methoxycarbonyl)methyl]amino}methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1c**). To a sol. of *Meldrum*'s acid (0.72 g, 5 mmol) in dry DMF (2 mL) in a glass ampoule, Et_3N (1.4 mL, 10 mmol) was added. Isothiocyanate **4c** [13] (0.655 g, 5 mmol) was added, and the ampoule was sealed. The ampoule was placed for 24 h at r.t. The mixture was poured into ice-cold aq.2 M HCl (15 mL). The solid precipitate was filtered and washed thoroughly with cold H_2O. The precipitate was dried in vaccum desicator over P_4O_{10} and used without further purification. Yield:

1.16 g (88 %) yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.77 (*s*, 6 H); 3.84 (*s*, 3 H); 4.36 (*d*, *J* = 5.2, 2 H); 11.61 (br. *s*, 1 H); 16.25 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 26.2, 46.5, 53.1, 83.9, 105.0, 163.6, 168.2, 172.9, 184.5. HRMS (ESI): calcd for $C_{10}H_{12}NO_6S$ $[M - H]^-$: 274.0384; found: 274.0395

5-(Mercapto{[(1-methoxycarbonyl)isobutyl]amino} methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1d**). To a sol. of *Meldrum*'s acid (0.72 g, 5 mmol) in dry DMF (2 mL) in a glass ampoule, Et_3N (1.4 mL, 10 mmol) was added. Isothiocyanate **4d** [13] (0.865 g, 5 mmol) was added, and the ampoule was sealed. The ampoule was placed for 24 h at r.t. The mixture was poured into ice-cold aq. 2 M HCl (15 mL). Resulted mixture was extracted with AcOEt(2 x 30mL), the org. layer was washed with brine (2 x 30mL) and with sat. aq. $NaHCO_3$ (2 x 30 mL). The alkaline layer was acidified with 2 M HCl and extracted with AcOEt (2 x 30mL), and the org. layer was dried ($MgSO_4$). After filtration, the solvents were removed under reduced pressure. The obtained yellow oil was used without further purification. Yield: 0.72 g (47 %). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.99 (*d*, *J* = 6.7, 3 H); 1.02 (*d*, *J* = 7.0, 3 H); 1.71 (*s*, 6 H); 2.30-2,37 (*m*, 1 H); 3.73 (*s*, 3 H); 4.60 (*dd*, *J* = 7.9, 4.8 Hz, 2 H); 11.62 (*d*, J = 7.9, 1 H); 15.93 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.3, 19.6, 26.1, 31.3, 52.7, 63.1, 83.7, 104.7, 163.1, 170.3, 183.9.

*Preparation of N,N'-disubstituted-thiomalonamides or pseudopeptide with retro-thioamide bond (**3aa-dg**).General procedure.* A sol. of **1** (2 mmol) and the corresponding amine or amino acid hydrochloride **2** (2 mmol) in an anh. solvent (ethylbenzene (A), 1,2-dichloroethane (B), toluene (C)) (10 mL) was stirred and heated to reflux for the time specified in the *Table*. After completion of the reaction, the solvent was removed under vaccum, and the residue was purified.

3-Anilino-N-phenyl-3-thioxopropanamide (**3aa**). Purification by crystallization from (AcOEt-hexane); M.p. 141-144°. ^{1}H-NMR (200 MHz, acetone-d_6): 4.08 (*s*, 2 H); 7.14-7.81 (*m*, 10 H); 8.51 (*s*, 1 H); 11.20 (*s*, 1 H). ^{13}C-NMR (50 MHz, acetone-d_6): 55.2, 119.4, 123.1, 123.7, 126.4, 128.8, 129.0, 139.2, 139.7, 165.8, 194.9. HRMS (ESI): calcd for $C_{15}H_{14}N_2OSN$ $[M + Na]^+$: 293.0725; found: 293.0731

3-(Methylamino)-N-(4-methylphenyl)-3-thioxopropanamide (**3bb**). Purification by crystallization from (EtOAc-hexane); M.p. 127-129 °C. ^{1}H-NMR

(500 MHz, $CDCl_3$): 2.34, (*s*, 3 H); 3.20 (*d*, *J* = 4.8, 3 H); 3.95 (*s*, 2 H); 7.14 (*d*, *J* =8.3, 2 H); 7.40 (*d*, *J* = 8.3, 2 H); 9.07 (*s*, 1 H); 9.79 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.2, 33.4, 53.0, 120.7, 129.8, 134.7, 135.1, 166.3, 196.0. HRMS (ESI): calcd for $C_{11}H_{14}N_2OSNa$ $[M + Na]^+$: 245.0725; found: 245.0730

N-(tert-Butyl)-3-(methylamino)-3-thioxopropanamide (**3bc**). Purification by flash column chromatography (AcOEt-hexane, 1:1); M.p. 115-118°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.38 (*s*, 9 H); 3.20 (*d*, *J* = 4.8, 3 H); 6.51 (*s*, 1 H); 9.97 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 28.8, 29.9, 33.2, 52.3, 167.9, 196.4. HRMS (ESI): calcd for $C_8H_{16}N_2OSNa$ $[M + Na]^+$: 211.0881; found: 211.0877.

N-Benzyl-3-(methylamino)-3-thioxopropanamide **(3bd).** Purification by crystallization from (AcOEt-hexane); M.p. 94-96°. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.19 (*d*, *J* = 4.8, 3 H); 3.77 (*s*, 2 H); 4.42 (*d*, *J* = 5.8 , 2 H); 7.15 (*s*, 1 H); 7.26-7.37 (*m*, 5 H); 9.80 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 33.3, 44.1, 51.8, 127.9, 128.0, 129.1, 137.4, 168.3, 195.9. HRMS (ESI): calcd for $C_{11}H_{14}N_2OSNa$ $[M + Na]^+$: 245.0725; found: 245.0721.

(2-p-Tolylcarbamoyl-thioacetylamino)-acetic acid methyl ester (**3cb**). Purification by flash column chromatography (AcOEt-hexane, 2:3); M.p. 105-107°. ^{1}H-NMR (500MHz, $CDCl_3$): 2.32 (*s*, 3 H); 3.80 (*s*, 3 H); 3.97 (*s*, 2 H); 4.43 (*d*, *J* = 4.8, 2 H); 7.12 (*d*, *J* = 7.81, 2 H); 7.40 (*d*, *J* = 7.81, 2 H); 8.69 (*s*, 1 H); 9.86 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$) 21.4, 47.8, 53.1, 53.2, 120.9, 129.9, 135.0, 135.2, 166.2, 169.1, 197.2. HRMS (ESI): calcd for $C_{13}H_{16}N_2O_3SNa$ $[M + Na]^+$: 303.0779; found: 303.0789.

[2-(Methoxycarbonylmethyl-thiocarbamoyl)-acetylamino]-acetic acid methyl ester (**3ce**). Purification by flash column chromatography (AcOEt-hexane, 7:2); orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.76 (s, 3 H); 3.79 (s, 3 H); 3.86 (s, 2 H); 4.07 (d, *J* = 5.5, 2 H); 4.43 (d, J = 4.8, 2 H); 7.28 (s, 1 H); 9.92 (s, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$) 41.3, 47.2, 50.7, 52.5, 168.1, 168.6, 169.8, 196.0. HRMS (ESI): calcd for $C_9H_{14}N_2O_5SNa$ $[M + Na]^+$: 285.0521; found: 285.0518.

2-[2-(Methoxycarbonylmethyl-thiocarbamoyl)-acetylamino]-propionic acid methyl ester **(3cf).** Purification by flash column chromatography (AcOEt-hexane, 2:1); M.p. 116-120°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.45 (d, *J* = 7.3 Hz, 3 H); 3.73 (s, 3 H); 3.78 (s, 3 H); 3.84 (s, 2 H); 4.42 (d, *J* = 4.9, 2 H); 4.53-4,59 (m, 1 H); 7.20 (d, *J*

= 6.3, 1 H); 9.99 (s, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$) 18.4, 47.8, 48.9, 51.4, 53.1, 168.0, 169.2, 173.5, 196.7. HRMS (ESI): calcd for $C_{10}H_{16}N_2O_5SNa$ $[M + Na]^+$: 299.0678; found: 299.0689

2-[2-(Methoxycarbonylmethyl-thiocarbamoyl)-acetylamino]-3-methyl-butyric acid methyl ester (**3cg**). Purification by flash column chromatography (AcOEt-hexane, 5:4); orange oil. ^{1}H-NMR (200MHz, $CDCl_3$): 0.92 (*d*, *J* = 3.9, 3 H); 0.95 (*d*, *J* = 3.9, 3 H); 2.14-2,20 (*m*, 1 H); 3.75 (*s*, 3 H); 3.79 (*s*, 3 H); 3.86 (*s*, 2 H); 4.46 (*d*, *J* = 4.9, 2 H); 4.49-4.56 (*m*, 1 H); 7.07 (*d*, *J* = 8.4, 1 H); 7.28 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$) 17.7, 18.8, 31.0, 47.2, 51.0, 52.1, 52.4, 57.4, 167.7, 168.5, 171.8, 196.2. HRMS (ESI): calcd for $C_{12}H_{20}N_2O_5SNa$ $[M + Na]^+$: 327.0991; found: 327.0999.

2-[2-(Methoxycarbonylmethyl-thiocarbamoyl)-acetylamino]-3-methyl-pentanoic acid methyl ester (**3ch**). Purification by flash column chromatography (AcOEt-hexane, 5:4); yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.92-0.94 (*m*, 6 H); 1.58-1.70 (*m*, 3 H); 3.74 (*s*, 3 H); 3.79 (*s*, 3 H); 3.84 (*s*, 2 H); 4.38-4.48 (*m*, 2 H); 4.57-4.61 (*m*, 1 H); 7.05 (*d*, *J* = 7.8, 1 H); 9.97 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 22.1, 23.0, 25.1, 41.3, 47.6, 51.2, 51.4, 52.7, 52.8, 168.0, 168.9, 173.3, 196.5. HRMS (ESI): calcd for $C_{13}H_{22}N_2O_5SNa$ $[M + Na]^+$: 341.1147; found: 341.1140.

2-[2-(Methoxycarbonylmethyl-carbamoyl)-thioacetylamino]-3-methyl-butyric acid methyl ester (**3de**). Purification by flash column chromatography (AcOEt-hexane, 5:4); yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.95 (*d*, *J* = 6.8, 3 H); 1.0 (*d*, *J* = 6.8, 3 H); 2.27-2.35 (*m*, 1 H); 3.72 (*s*, 3 H); 3.85 (*d*, *J* = 6.3, 2 H); 4.03 (*d*, *J* = 5.4, 2 H); 4.95-4.98 (*m*, 1 H); 7.38 (*s*, 1 H); 9.95 (*d*, *J* = 7.32, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$) 18.9, 19.2, 31.2, 41.8, 51.1, 52.7, 52.9, 64.0, 169.1, 170.4, 171.2, 196.6. HRMS (ESI): calcd for $C_{12}H_{20}N_2O_5SNa$ $[M + Na]^+$: 327.0991; found: 327.1002.

2-(2-Acetylamino-ethylcarbamoyl)-thioacetylamino]-acetic acid methyl ester (**3ci**). Purification by flash column chromatography (AcOEt-hexane, 5:4); M.p. 130-134°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.04 (*s*, 3 H); 3.44 (*s*, 4 H); 3.81 (*s*, 3 H); 3.82 (*s*, 2 H); 4.46 (*d*, *J* = 4.8, 2 H); 6.89 (*s*, 1 H); 7.48 (*s*, 1 H); 10.10 (*s*, 1 H). ^{13}C-NMR (50

MHz, $CDCl_3$) 22.5, 39.0, 39.4, 47.1, 51.7, 52.5, 168.9, 169.3, 172.5, 197.9. HRMS (ESI): calcd for $C_{10}H_{17}N_3O_4SNa$ $[M + Na]^+$: 298.0836; found: 298.0861.

2-[2-(2-Acetylamino-ethylcarbamoyl)-thioacetylamino]-3-methyl-butyric acid methyl ester (**3di**). Purification by flash column chromatography (AcOEt-hexane, 5:4); oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*d*, *J* = 6.8, 3 H); 1.07 (*d*, *J* = 6.8, 3 H); 2.00 (*s*, 3 H); 2.33- 2.40 (*m*, 1 H); 3.33-3.49 (*m*, 4 H); 3.78 (*s*, 3 H); 3.80 (*s*, 2 H); 4.96-4.98 (*m*, 1 H); 6.71 (*s*, 1 H); 7.48 (*s*, 1 H); 10.07 (*d*, *J* = 6.84, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.8, 19.2, 23.4, 30.8, 39.7, 40.1, 51.7, 52.6, 64.0, 169.3, 171.4, 171.9, 197.1. HRMS (ESI): calcd for $C_{13}H_{23}N_3O_4SNa$ $[M + Na]^+$: 340.1307; found: 340.1302.

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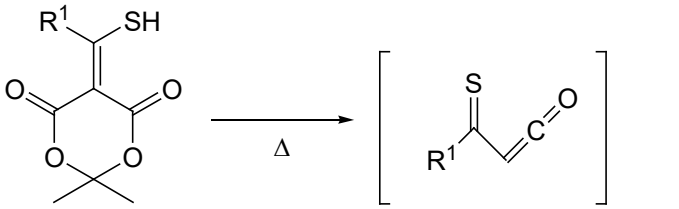
Scheme 1

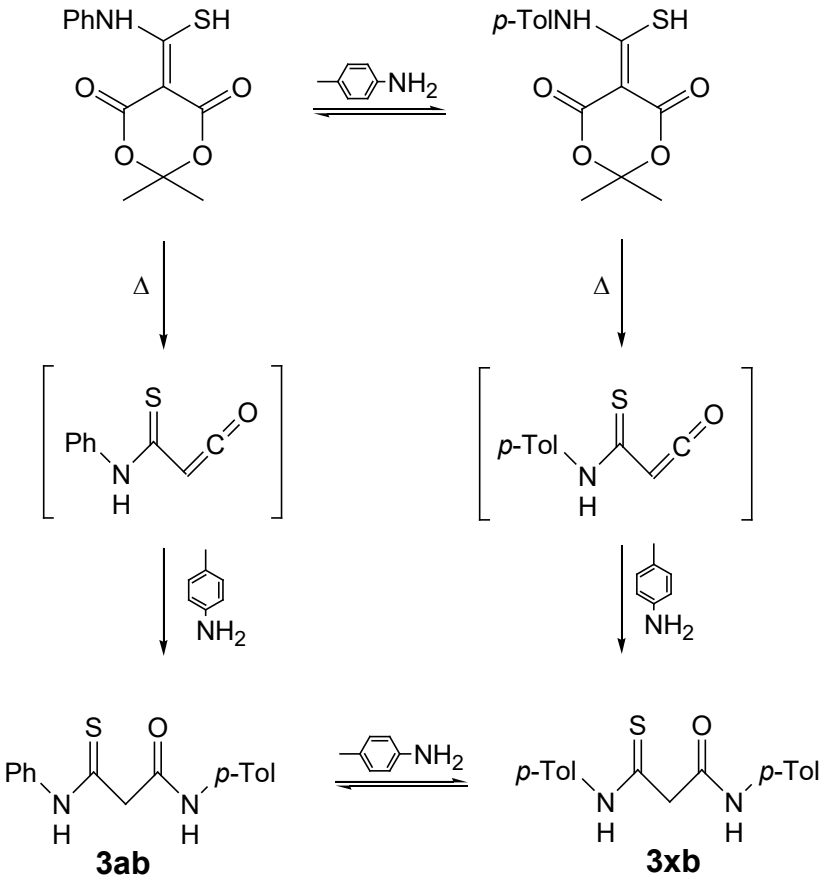


1a R^1 = PhNH
1b R^1 = MeNH
1c R^1 = MeOGly
1d R^1 = MeOVal

HAA^2OMe
2e-i

pseudopeptides **3ce-di**

Scheme 2



Scheme 3

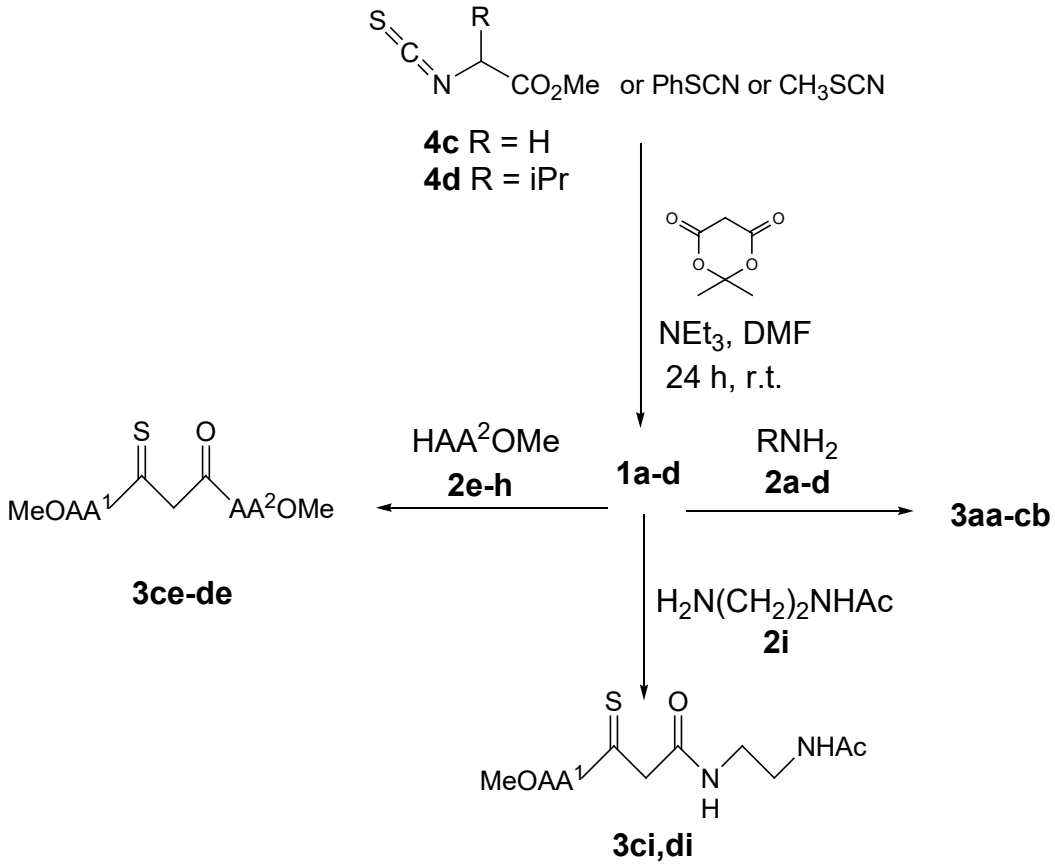


Table. Reactions of Thiocarbamoyl Meldrum's Acid with Nucleophiles.

Entry	**1**	R^1	**2**	H-Nu	Product **3**	Solvent[a]	Time (h)	Yield (%)
1[b]	**a**	NHPh	**a**	H-NHPh	**3aa**	A	0.6	79
2[b]	**a**	NHPh	**b**	H-NH-p-Tol	**3ab** + **3xb**	A	0.6	-[c]
3	**b**	$NHCH_3$	**b**	H-NH-p-Tol	**3bb**	A	1	100
4	**b**	$NHCH_3$	**c**	H-NH-*t*-Bu	**3bc**	A	1	99
5	**b**	$NHCH_3$	**d**	H-NH-Bzl	**3bd**	A	1	75
6	**c**	-GlyOMe	b	H-NH-p-Tol	**3cb**	B	4.1	68
7	**c**	-GlyOMe	e	H-GlyOMe	**3ce**	B	6	50
8	**c**	-GlyOMe	f	H-AlaOMe	**3cf**	B	6.5	62
9	**c**	-GlyOMe	f	H-AlaOMe	**3cf**	C	1.1	58
10	**c**	-GlyOMe	g	H-ValOMe	**3cg**	B	5.5	49
11	**c**	-GlyOMe	h	H-LeuOMe	**3ch**	B	5.5	71
12	**d**	-ValOMe	e	H-GlyOMe	**3de**	B	7	50
13[d]	**c**	-GlyOMe	f	H-AlaOMe	**3cf**	B	6.5	51
14	**c**	-GlyOMe	i	$H\text{-}NHCH_2CH_2NHAc$	**3ci**	B	18	33
15[d]	**c**	-GlyOMe	i	$H\text{-}NHCH_2CH_2NHAc$	**3ci**	B	18	70
16[d]	**d**	-ValOMe	i	$H\text{-}NHCH_2CH_2NHAc$	**3di**	B	22.5	73

[a]) Solvent A = ethylbenzene, B = 1,2-dichloroethane, C = toluene.[b]) **2** (2 equiv.) was used. [c]) Mixture of two products. [d]) TMSCl (2 equiv.) was used

Graphical Abstarct.